

**Cognitive, social and emotional processes in
unawareness of illness following stroke**

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*For Baby Besharati,
who stuck it out with me while I finished this PhD baby.*

Abstract

Disturbances in unawareness can offer an important avenue to investigate the neurocognitive processes involved in the construction of the bodily self. The general aim of the present thesis was to advance the current state of knowledge on a prototypical disorder of self-awareness, anosognosia for hemiplegia (AHP): unawareness of motor deficits contralateral to a brain lesion. Based on insights gained from both clinical and experimental research on anosognosia, it is argued that purely sensorimotor accounts do not explain several features of the syndrome, such as the delusional and emotional aspects. Therefore a revision of prevailing, modular theories of anosognosia is proposed that take into account the involvement of affective and social processes. Accordingly, the thesis aimed to: (1) investigate the emotional and social factors that underlie motor unawareness; (2) identify the neurocognitive factors and neuroanatomical correlate that underlie such factors; and (3) develop potential, bedside rehabilitation interventions for AHP that are informed by the above investigations.

These aims were achieved using an integrative methodological approach, which combined neuropsychological testing, psychophysiological experiments and neuroimaging methods. A series of experimental group investigations and clinical case studies were conducted in 53 adult patients with right-hemisphere strokes. The main results of these studies showed that: (i) motor awareness is modulated by negative, but not positive emotion in a social context; (ii) anosognosia is associated with specific deficits in 3rd person perspective taking in visual-spatial and mentalising tasks; (iii) anosognosia is modulated by ‘other’ referent and 3rd person verbal and visual perspective taking. These experimental findings on the role of emotion and social processes in AHP were in turn used to develop a rehabilitation intervention applied in two case studies that showed promising results. Additionally, converging neuroimaging evidence provided support for the unique involvement of the inferior frontal gyrus, insula ribbon, supramarginal and superior temporal gyrus, and dorsal frontal white matter in anosognosia, which have well-established links to motor monitoring, subjecting feelings and self awareness, and the proposed ‘mentalising network’. These finding are in support of a proposed new account of AHP, which moves away from traditional modular theories of anosognosia, towards a dynamic model of the construction of the bodily self.

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List of Abbreviations

| Abbreviation | Meaning |
|--------------|---|
| AHP | Anosognosia for hemiplegia |
| HP | Hemiplegic |
| CT | Computed tomography |
| MRI | Magnetic resonance imaging |
| VLSM | Voxel-base lesion symptom mapping |
| ROI | Region of interest |
| VSPT | Visual-spatial perspective taking |
| MRC | Medical research council scale |
| HADS | Hospital depression and anxiety scale |
| BIT | Behavioural inattention test |
| FAB | Frontal assessment battery |
| MOCA | Montreal cognitive assessment |
| ToM | Theory of mind |
| PPT | Person perspective taking |
| PP | Perspective taking |
| IFG | Inferior frontal gyrus |
| MFG | Middle frontal gyrus |
| TPJ | Temporal parietal junction |
| STG | Superior temporal gyrus |
| SMG | Supramarginal gyrus |
| MCA | Middle cerebral artery |
| ADL | Activities of daily living |
| LUL | Left upper limb |
| LLL | Left lower limb |
| VATA-m | Visual-Analogue Test for anosognosia for motor deficits |
| JAT | Judgment of Actions Test |
| UM | Unimanual |
| BM | Bimanual |
| BP | Bipedal |
| AD | Alzheimer's disease |
| DTI | Diffusion tensor imaging |

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These publications form part of Chapters 3 and 6.

Statement of contribution

The student was responsible for the literature search and review; concept and design of the studies; the patient recruitment, testing and data collection; performing data analysis, including both statistical and neuroimaging analysis, as well as the interpretation of results; and writing of the thesis.

Chapter 1 Introduction

1.1 Introduction

Conceptualising conscious awareness as a subjective, first-person, phenomenon has often resulted in the marginalisation of its scientific enquiry (Damasio, 1998; Prigatano, 2010). Nevertheless, disturbances of self-awareness have fascinated relevant clinical fields such as neurology and psychiatry since the time of Charcot, Freud and Babinski. Nowadays, it is recognised that neuropsychiatric disturbances of awareness offer an important avenue to investigate the neurocognitive processes involved in the construction of the self (Fotopoulou, 2012). Particularly in regards to the bodily self, the classical work of William James (1890) describes the immediacy of experiences of one's own body, while differentiating between different senses of the self. Within this framework, self-awareness involves both a *sense of ownership*- the feeling that my body belongs to me; and *sense of agency*- the feeling that I am the initiator of an action (Gallagher, 2000). Consequently disorders of self-awareness can involve disturbances of body ownership or agency, or both. Disorders of *Body ownership* include: asomatognosia, the inability to recognise one's own body (Cutting, 1978) and somatoparaphrenia, a set of body ownership delusions where patients attribute ownership of their arm to another person, often a close relative (Gerstmann, 1942).

This thesis will focus on a specific disturbance of *body agency* called anosognosia for hemiplegia (AHP), the apparent unawareness of or, inability to understand paralysis and other sensorimotor deficits following stroke (Cocchini, Beschin, Cameron, Fotopoulou, & Della Sala, 2009). More specifically, this thesis aims to investigate how neurological patients represent and emotionally perceive themselves and their bodies following brain injury (i.e. stroke). AHP is a prototypical form of unawareness, and can provide useful clinical and empirical insights, as well as the neural basis, of bodily self-awareness. Previous research has focused mostly on cognitive and motor models (Frith, 2000; Garbarini et al., 2012; Vallar & Ronchi, 2006). Although still theoretically important, pure motor accounts of AHP have neglected the delusional and emotional aspects of the phenomenon (Turnbull & Solms, 2005). Previously, limited experimental research (e.g. Fotopoulou, Pernigo, Maeda, Rudd, & Kopelman, 2010; Turnbull, Evans, & Owen, 2005) and clinical case studies (e.g. Kaplan-Solms & Solms, 2000) have focused on the potential influence of emotional and social factors on anosognosia. The purpose of this

thesis is to examine the cognitive, emotional and social processes underlying anosognosia for motor deficits.

Accordingly, the present thesis aimed to contribute to experimental and neuroimaging research into the emotional and social factors that modulate AHP. To address these main aims, the thesis used a combination of methods from clinical neuropsychology and behavioural neurology, experimental psychology and social cognitive neuroscience, to combine methodological and theoretical approaches in a novel interdisciplinary way. This introductory chapter briefly describes the conceptualisation of anosognosia, provides an overview of the clinical presentation and incidences, as well as the diagnosis and assessment of AHP. It will cover neuroanatomical and neuropsychological findings and possible causes, as well as outline the main theoretical frameworks and models describing the phenomena. It will then move to discuss the potential for rehabilitation interventions for AHP. The chapter will conclude with a summary of the specific objectives and research questions of this thesis, and provide an outline of the following chapters.

1.2 Conceptualising anosognosia

The first documented descriptions of anosognosia were made by Von Monakow (1885), Anton (1898) and Pick (1898; also see Bisiach & Gemainiani, 1991 and Prigatano, 2010). Babinski (1914) initially coined the term anosognosia (a: without; noso: disease; gnosis: knowledge) a century ago to describe unawareness of paralysis following stroke. The term however, is now used more broadly to include unawareness in many neuropathology's, including traumatic brain injury (Prigatano, 1988), Alzheimer's disease (Reed, Jagust, & Coulter, 1993) and schizophrenia (Mohamed, Fleming, Penn & Spaulding, 1999). There is currently a lack of consensus in the literature on the actual definition of anosognosia (see Table 1.1). However for the purpose of this thesis anosognosia for hemiplegia will be operationally defined as: the apparent unawareness or inability to understand paralysis and other sensorimotor deficits following stroke (Cocchini et al., 2009).

Table 1.1 *Defining anosognosia*

| Authors | Definitions of Anosognosia |
|---|--|
| Babinski (1914) | The apparent lack of awareness of hemiplegia following an acute brain lesion |
| Cutting (1978) | Denial of limb weakness, including other “anosognosia phenomena” (i.e. abnormal attitudes towards limb weakness) |
| Prigatano & Schacter (1991) Prigatano (2010) | Unawareness for motor, visual or cognitive impairments in patients with neurological diseases |
| Orfei et al., (2007) | A disorder in which a patient, affected by a brain dysfunction, does not recognise the presence or appreciate the severity of deficits in sensory, perceptual, motor, affective or cognitive functioning |
| Cocchini et al. (2009) | Apparent unawareness/inability to understand paralysis and other sensorimotor deficits following stroke |

1.3 Clinical presentation

The following clinical vignettes provide narrative examples of the variations in the clinical presentation of the phenomenon. The case examples are of right-handed, female patients who both suffered a stroke in the region of the right middle cerebral artery. The interviews were conducted by the investigator (SB) three days post onset.

1.3.1 Case example 1

SB: Why are you in the hospital?

Patient: They say I had a stroke, but I don't remember anything about it.

SB: The doctors tell me you had a stroke, do you agree with them?

Patient: I don't know anything about strokes.

SB: What kind of symptoms have you noticed since you came to the hospital?

Patient: I haven't noticed anything really.

SB: Do you have any weakness anywhere?

Patient: Not really, I'm sure I can make a fist if I wanted to.

SB: Is your left arm causing you any trouble?

Patient: Not at all, no.

SB: [The examiner lifts the patient's left arm and moves it to the right hemispace] There seems to be some weakness in you left arm, do you agree?

Patient: No it's fine.

SB: Can you try and move your left arm for me?

Patient: Yes, I move it.

SB: But I didn't see your left arm move.

Patient: That's because you weren't paying attention, I just moved it now!

1.3.2 Case example 2

SB: What symptoms have you noticed since the stroke? How does your body feel?

Patient: It feels alright.

SB: Do you have any weakness anywhere in your body?

Patient: No, no weakness.

SB: Is your left arm causing you any trouble?

Patient: No, of course not.

SB: Can you raise your left leg?

Patient: Yeah, sure I can.

SB: Can you please try and raise your left arm for me?

Patient: [Silence. The patient does not move.]

SB: Can you try and do it for me now?

Patient: [Patient uses right arm to move left arm]

SB: Did you do it?

Patient: Yes, you saw it move.

SB: Yes, but did it move on it's own?

Patient: Well, with the help of this [right] one [arm].

SB: Can you do it without the help of your right hand?

Patient: Yeah.

SB: Do you think you can clap your hands?

Patient: Yes, sure.

SB: Can you please show me?

Patient: [Uses right hand to lift left hand, then slaps the top of the left had to ‘clap’]

SB: Did you manage to clap your hands?

Patient: Yes, I did it. [The patient then winks at SB]

As the clinical examples demonstrate, AHP presents in different forms and it is important to try to differentiate between the potential varieties of AHP in both classifying patients and when investigating the underlying mechanisms involved (for discussion see Vocat, Staub, Stroppini, & Vuilleumier, 2010). In the literature, characteristics like the *degree* (i.e. severity of unawareness symptoms), *extension* (i.e. the extent of unawareness of motor weakness, such as admitting to hemiplegia but underestimating the functional significance), *partiality* (i.e. if patients have partial knowledge or awareness of their motor weakness) and *specificity* (i.e. how specific is their unawareness; are patients only unaware of their paralysis or does unawareness generalise to other disabilities or illnesses) of unawareness, as well as the affectivity towards the paralysed body part and its sense of *ownership* have been noted to vary (see Table 1.2 for summary; Jenkinson, Haggard, Ferreira, & Fotopoulou, 2013; Marcel, Tegnér, & Nimmo-Smith, 2004; Prigatano & Schacter, 1991). Specifically in terms of the degree of AHP, unawareness can vary in severity ranging from a mere indifference to one’s disabilities or illness, usually referred to as anosodiaphoria (Babinski, 1914), to blatant denial of limb paralysis and delusional beliefs of ability. Patients may also report illusionary movements-claiming their limb has moved despite demonstration of the opposite. Illusory limb movements are also commonly associated with reported false memories (e.g. “I just walked to the bathroom myself, I’m just too tired to show you now”).

In terms of extension, some patients deny their motor deficits in every aspect tested, while others may verbally accept their deficit, but fail to acknowledge their functional consequences (e.g. they try to stand and walk), or vice versa. Differences in partiality are suggested by studies (Cocchini, Beschin, Fotopoulou, & Della Sala, 2010; Fotopoulou et al., 2010; Moro, Pernigo, Zapparoli, Cordioli, & Aglioti, 2011) that show that some but not all patients present with either explicit, or, implicit awareness of their deficits (‘implicit’ awareness is defined as ‘knowledge that is expressed in task performances unintentionally and with little or no phenomenal awareness’; Schacter, 1990, p. 157). There has been recent evidence suggesting that some patients with AHP show greater motor awareness in 3rd person perspective as opposed to 1st person perspective taking

tasks, both when visually presented in videos (Fotopoulou, Rudd, Holmes, & Kopelman, 2009) and verbally (Marcel et al., 2004).

Moreover, the specificity of unawareness can vary, in that some patients only deny their hemiplegia, while accepting other stroke-induced deficits, while other patients deny all stroke-related deficits. Some patients may also show a morbid dislike or hatred for their paralysed limb (i.e. misoplegia; Critchley, 1955, 1974) as opposed to the opposite emotional response, anosodiaphoria (Babinski, 1914). Finally, only a subset of AHP patients may also present with disruptions in their own sense of body ownership, asomatognosia (the inability to recognise one's own body), or somatoparaphrenia (bodily ownership delusions; Gerstmann, 1942). This clinical variability suggests that AHP is a multifaceted and heterogeneous phenomenon, but this position remains debated in the literature.

Table 1.2 *Variations in clinical presentation of anosognosia*

| Presentation | Description |
|----------------------|--|
| Degree & Affectivity | Range of severity: emotional indifference (anosodiaphoria) to denial & delusional beliefs; hate of paralysed limb (misoplegia) |
| Extension | Verbally acknowledge deficits but not functional consequences (e.g. try to walk) & visa versa |
| Partiality | Partial knowledge or awareness of motor deficits, e.g. explicit versus implicit awareness |
| Specificity | Generalised unawareness of illness (or stroke related symptoms), or deny only hemiplegia |
| Ownership | Body ownership delusions (somatoparaphrenia); rejecting ownership of limb (asomatognosia) |

1.4 Assessment

A number of assessment measures have been designed to assess AHP. The disparity between the tests however has resulted in vague diagnostic criteria and prevented a single ‘gold standard’ assessment from being developed (Jenkinson, Preston, & Ellis, 2011; Orfei et al., 2007, for review). Cutting (1978) was one of the first to introduce a formal assessment measure of anosognosia and related phenomena. His detailed questionnaire proved to be a useful supplement to clinical observations. Clinical assessments further improved by introducing the use of a frequently used 4-point scale, used by the clinician to quantify the severity of the patient’s unawareness and ultimately classified as mild, moderate or severe (Bisiach, Vallar, Perani, Papagno, & Berti, 1986). The scale serves to differentiate between patients who are unaware of their paralysis, but recognise their deficit when asked and are unable to perform a specific movement, from patients who hold an active delusional component of anosognosia, producing false beliefs of having moved their hemiplegic limb.

A more sensitive measure was later developed to assess the relationship between verbal anosognosia and related confabulations (Feinberg, Roane & Ali, 2000). This ‘Feinberg et al. interview’, consisting of 10 questions, not only determines the severity of unawareness, but identifies the presence of illusionary movements. A shortcoming of both the Bisiach scale and the Feinberg et al. interview is their reliance on explicit and verbal means of assessment. The Berti, Ladavas and Corte (1996) interview provides a measure of both implicit and explicit awareness, and differentiates between unawareness for lower and upper limb paralysis, using both verbal and behavioural responses. The interview also estimates awareness of current motor ability in activities of daily living (e.g. clapping hands and walking). Many other assessment methods have more recently been developed (see Cocchini et al., 2010; Della Sala et al., 2009; Marcel et al., 2004; Starkstein et al., 2006) to assess and classify anosognosia more reliably. These methods assess the clinical variability of AHP in greater detail and hold the potential for better diagnostic accuracy and homogeneity in the field. Yet despite this progress, it is clear that further psychometric testing and validation is needed to help define the diagnostic and assessment criteria for AHP (Jenkinson et al., 2011; Orfei et al., 2007). An important aim of clinical research in AHP is not just to identify the presence or absence of unawareness of motor paralysis (see next section), but also to understand the multidimensional nature of the phenomenon (Vocat et al., 2010). In order to help refine already existing assessment methods and develop new tools, innovative and dedicated research on the

clinical variability of AHP is needed, as well as a disciplinary move away from binary distinctions and towards multifactorial criteria.

1.5 Incidence and duration

AHP occurs more frequently following right perisylvian lesions, and less often in left perisylvian lesions (Cocchini et al., 2009; Heilman, Barrett, & Adair, 1998; Nathanson, Bergman & Gorden, 1952). A wide range of frequencies have been reported on the prevalence of anosognosia for hemiplegia. These variations can mostly be attributed to difference in diagnostic criteria, time and type of assessment (also see above) and variations in patient recruitment and selection (Orfei, Caltagirone, & Spalletta, 2009). Initial studies reported a frequency of 33 to 58% of AHP in stroke patients (Cutting, 1978; Bisiach et al., 1986), more recently however a meta-analysis of studies reported a frequency ranging from 20 to 44% depending on the time of assessment (Pia, Neppi-Modona, Ricci, & Berti, 2004). Orfei's et al. (2007) review further identified a prevalence of 7 to 77%. However, Baier and Karnath (2005) used a more sensitive measure of AHP, only classifying patients as anosognosic after scoring a minimum of 2 on the Bisiach scale (i.e., the disorder is acknowledged only after demonstration of paralysis, Bisiach et al., 1986). Consequently, a much lower rate of AHP was reported: 10-18% in acute and subacute patients. In the first longitudinal study on AHP, the evolution of unawareness overtime was documented in 58 right-hemisphere patients assessed at three different time intervals: 3 days (hyperacute), 1 week (subacute) and 6 months (chronic). They reported a frequency of 38% in the hyperacute stage, dropping to 18% after 1 week and only 5% remaining aware in the chronic stage.

Cocchini and Della Sala (2010) however, suggest that both low incidence of anosognosia in the chronic phase and following left-hemisphere damage may be a result of poor diagnostic tools used. Patients for example, may have actually “learned” the “correct” response after repeated awareness questions, rather than having a genuine remission of their unawareness. The “true” incidence of anosognosia in left-hemisphere brain damaged patients may also be obstructed by dependency on language abilities in awareness assessments. This has resulted in a recently developed tool, the Visual-Analogue Test for Anosognosia for motor impairment (VATA-m), which is designed to assess anosognosia with aphasic patients (Della Sala et al., 2009). Using this tool, this group has indeed noted that anosognosia in aphasic patients may be commonly underreported due to verbal assessment constraints.

1.6 Etiology of anosognosia

The precise neurological and psychological causes of AHP have been difficult to establish. It has however been mostly accepted (Marcel et al., 2004; Orfei et al., 2007; Vocat et al., 2010) that a combination of a number of factors, rather than a single deficit, is likely to account for the range of clinical presentations and variability in anosognosia (Vuilleumier, 2004; Vocat et al., 2010). Yet the precise neurological and psychological causes and their critical combination remain unclear. Below a review of the major neuroanatomical and neuropsychological explanations of AHP to date is presented.

1.6.1 Neuroanatomical accounts

Recent improvements in structural neuroimaging methods, software and analysis, have resulted in several new studies that attempt to identify the precise brain regions that are associated with AHP. However this has resulted in the identification of multiple lesions sites, and sometimes opposing findings. This can be accounted for by the often fluctuating and wide variability found in unaware patients, but also by the scan quality (e.g. use of computed tomography, CT, versus magnetic resonance imaging, MRI), lesion mapping methods and analysis, and the diagnostic criteria and tests used (Jenkinson et al., 2011).

Taking into account reported findings from both CT and MRI scans, Pia et al. (2004) conducted a meta-analysis using 85 AHP cases. The lesion sites identified included the frontal, parietal, temporal, and occipital cortical regions, and at a subcortical level the thalamus, basal ganglia, internal capsule, corona radiata, insula, lateral ventriculus, and amygdalae. Their results further suggested that at a cortical level frontoparietal damage was the most frequent lesion site, and basal ganglia and thalamus lesions being most likely to account for unawareness following damage to a single subcortical area. A combination of both cortical and subcortical structures was therefore found to play a significant role in causing unawareness.

Damage to areas related to motor planning and the role of the insula in AHP has recently become a center of much interest and debate in the literature. In a lesion analysis study Karnath, Baier, & Nägele (2005) analysed both CT and MRI scans of 27 patients: 14 with both hemiplegia and AHP patients, and 13 with only hemiplegia (HP control group). Both control and experimental groups were matched for age, lesion size and acuity, degree of hemiparesis, severity of neglect, sensory loss and visual fields deficits. The lesions were

mapped using MRIcon software on slices of a T1-weighted template MRI scan. The right posterior insula was identified as the only structure with greater damage in AHP patients. This runs in parallel to Craig (2009; 2002) model of self-awareness, in which he identifies the anterior insular cortex as the centre for all subjective feelings and self-awareness. In contrast, a lesion mapping study using both CT and MRI scans conducted by Berti et al. (2005) compared three patient groups: 17 patients with AHP, unilateral neglect and left hemiplegia (experimental group); 12 patients with unilateral neglect and left hemiplegia, and no AHP (control group); and 1 patient with left hemiplegia and AHP, and no unilateral neglect (case-study of 'pure anosognosia'). They studied the anatomical distribution of lesions by superimposing the lesion plots of the two groups and conducting an anatomical chi-square distribution of the comparison. Their analysis concluded that anosognosia is characterised by damage to the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG; dorsal premotor areas, Brodmann's areas 6 and 44 specifically), the postcentral gyrus (somatosensory cortex), the precentral gyrus (primary motor cortex; Brodmann's area 4), the insula ribbon, Brodmann's area 46 (frontal agranular cortex) and sometimes in the dorsolateral prefrontal cortex. When compared to the case-study of 'pure anosognosia', the same areas were identified with the exception of the dorsolateral prefrontal cortex, and the addition of the insula. Areas related to motor monitoring were therefore identified as the most important indicators of anosognosia. The results of Vocat & Vuilleumier's (2010) longitudinal study describe in detail above, also used CT and MRI scans to conduct an anatomical lesion analysis using a voxel based statistical mapping method (voxel-based lesion symptom mapping, VLSM). In the hyperacute phase (3 days post stroke) insula damage and adjacent subcortical features were identified, similar to those reported by Karnath et al. (2005). While the persistence of AHP into the sub-acute and chronic stage was associated with lesions to the IFG and MFG (premotor areas), cingulate gyrus, parietotemporal junction and medial temporal structures, which are inline with Berti et al. (2005) findings supporting the crucial role of the premotor cortex.

Fotopoulou et al. (2010) also conducted a lesion analysis using patient's CT and MRI scans, but uniquely correlated experimental data with lesion data. They used experimental results to identify and group patients into those with "implicit" awareness and "explicit" awareness, and compared them to a group of hemiplegic controls patients with hemispatial neglect, but no AHP. They aimed to identify the brain areas involved with different types of AHP (see Section 1.3 on clinical presentation), specifically the neural

correlates related to implicit and explicit awareness. Cortical areas, mostly the frontal, parietal and occipital lobes, were more frequently damaged in patients that had both implicit and explicit awareness. Interestingly, the insular cortex was more frequently damaged in patients with intact implicit awareness, but without explicit awareness. These results demonstrate the apparent neural dissociation between implicit and explicit awareness, therefore suggesting that clinical variability found in AHP may be associated with different lesion sites.

In support of these findings, Moro et al. (2011) similarly conducted a lesion mapping study in order to identify different neural structures involved in different types of anosognosia (i.e. implicit and explicit awareness). Twelve patients with severe hemiplegia and AHP were compared to a control group of 12 hemiplegic patients with no AHP. Lesions from CT and MRI scans were analysed using VLSM comparing damaged areas in anosognosic and non-anosognosic patients. They further identified the lesional correlates of patients with deficits in implicit and explicit awareness. Similar to Fotopoulou et al. (2010) impaired implicit awareness was associated with damage to subcortical areas including the basal ganglia, and impaired explicit awareness is more frequently related to cortical regions, including the frontal, temporal and parietal structures.

The most recent study to investigate the neural correlates of AHP was conducted with 35 acute (first 48 hours) right hemisphere damaged patients (Kortte, McWhorter, Pawlar, Slentz, Sur & Hills, 2014). Eight of these patients were classified as having severe AHP based on a cut-off score specified by Baier and Karnath (2005). The study aimed to identify cortical and subcortical structures associated with AHP in acute stroke patients using clinically acquired MRI scans and behavioural scores. The lesion analysis was conducted using a Region of Interest (ROI) analysis, with the results being confirmed by a secondary whole brain voxel-wise analysis. The study's findings provided support for the unique role of right IFG. The right IFG, also known as the frontal operculum, is made up of pars orbitalis (BA 47), pars opercularis (BA44) and pars triangularis (BA 45). The results indicated that BA area 47 (pars orbitalis) of the IFG was damaged in six out of the eight AHP patients, with no control (aware) patients having tissue abnormalities in that area. Right BA 44 (pars opercularis) and 45 (pars triangularis) of the IFG were also found to be more frequently lesioned in AHP patients compared to controls.

Taken together, there have been recent advances in our understanding of the neural correlates of anosognosia. However, multiple brain structures have been implicated with few firm conclusions provided. This is due to several factors, including the use of poor quality clinical scans, small sample sizes and differences in diagnostic criteria for AHP, as well as discrepancies in time of AHP assessment and brain scanning. Nevertheless, most studies have confirmed the pivotal role of the right-hemisphere in AHP. Several studies have provided converging evidence for the importance of premotor areas (IFG) and the insula ribbon, more generally frontoparietal damage, and to some extent subcortical structures, specifically the basal ganglia. Overall, evidence suggests that a combination of both cortical and subcortical structures are involved in causing motor unawareness.

Furthermore, the lesion mapping procedures used in most of the above studies do not draw on advanced statistical methods, but rather on meta-analysis approach (Pia et al., 2004), descriptive (lesion-overlay and subtraction plots) approach (Karnath et al., 2005) or binomial tests (e.g. Chi-square; Berti et al., 2005). Few studies have utilised advanced statistical methods, such as VLSM (Vocat et al., 2010) and ROI analysis (Kortte et al., 2014), to identify the statistical relationship between tissue damage and behaviour. Importantly, most previous studies have also relied on a priori classification of patients into groups based on lesion or behavioural scores that indicate a cut-off for pathology. In contrast the VLSM approach avoids this bias by not grouping patients based on lesion or behavioural cut-off scores, but rather by using continuous lesion and behavioural scores on a voxel-by-voxel basis (Bates et al., 2003). Nevertheless, mostly all of the above studies have only analysed the relationship between brain damage and behavioural scores indicating a diagnosis of AHP. Only two studies (Fotopoulou et al., 2010; Moro et al., 2011) uniquely correlated other behavioural findings from experimental data (e.g. implicit awareness experiments) with lesion data. The current study aimed to utilise recent methodological advances in lesion mapping methods, such as software and analysis procedures, to help specify the exact brain areas associated with anosognosia. Furthermore, it will use lesion data to investigate not only the anatomical areas associated with a diagnosis of AHP, but also with performance on experimental tasks designed to examine the role of emotion and social processes in anosognosia.

1.6.2 Neuropsychological accounts

1.6.2.1 Sensory and motor explanations

Early accounts of AHP regarded the phenomenon to be a secondary consequence of sensory deficits, specifically neglect (visual and tactile), which often co-occurs with AHP in right-hemisphere damage (Cutting, 1978; Levine, Calvanio, & Rinn, 1991). It was also suggested that a combination of sensory deficits and other higher-order functions (e.g. memory and confabulation) result in AHP (Berti et al., 1996; Levine, 1991). However, a series of studies have since shown double dissociations between AHP and primary or high-order sensory deficits and a number of other higher-order cognitive deficits (Bisiach et al., 1986; see Heilman & Harciarek, 2010 for review), showing that these deficits may not be necessary for its occurrence. It is nevertheless probable that the aforementioned factors can lead to greater severity of unawareness or predispose patients to AHP when other contributing factors are also present (Marcel et al., 2004; Fotopoulou, 2014). Therefore evidence suggests that other deficits, such as neglect, impairments in somatosensory functioning (e.g. proprioception), cognitive deficits (e.g. memory) can co-occur with AHP, but are not necessary for and do not explain the phenomena (Bisiach et al., 1986; Vocat et al., 2010; Korte et al., 2014).

More recent accounts have emphasised issues of motor planning and monitoring, rather than sensory deficits. Established computational models of the motor system proposed that motor awareness is dependent on the comparison between predicted and actual sensory information (Miall & Wolpert, 1996). Various studies have attempted to explain anosognosia using such models of motor control and awareness. It has been thus influentially proposed that AHP results from a specific deficit of *forward motor monitoring* (Heilman, Barrett & Adair, 1998; also see Berti et al., 2005; Frith, Blakemore & Wolpert, 2000). Interestingly from a neuroanatomical perspective, the right IFG is involved in action monitoring, but has also been associated with AHP (Berti et al., 2005; Korte et al., 2014). Here it is argued that there is an inconsistency in the predicted movement- based on intentions; and actual movement- based on sensory feedback. This mechanism has also been labeled as the *efferece copy* hypothesis (Frith, 2000; Frith, Blakemore & Wolpert; Jenkinson & Fotopoulou, 2010). According to this hypothesis AHP patients fail to correct cognitive predictions arising from their *intentions* to move their left arm or leg (Berti et al., 2005; Fotopoulou et al., 2008). Therefore, they fail to update efferent copies of their actions, despite mismatching afferent (e.g. visual or tactile)

information. Furthermore, it has been suggested that lesions to the premotor and somatosensory cortex, as well as the primary cortex and insula, lead to this misrepresentation between the intention to move and the actual movement (Berti et al., 2005; Karnath et al., 2005).

Fotopoulou et al. (2008) investigated these proposals experimentally using realistic prosthetic hands to generate visual feedback of movements in AHP patients, while manipulating whether they had the intention to move themselves (self-intention) or someone else would move their arms (other intention). Their results showed that in AHP the illusory perception of movement in a non-moving hand occurred significantly more often in self- versus other- intention trials. This therefore reflects an abnormal dominance of motor intentions about the predicted effects of the movement over visual sensory information about the actual effects of the movement. In addition, a recent study by Garbarini et al. (2012) provides a behavioural demonstration of intact motor intentions in AHP. Garbarini and colleagues compared the performance on a classical bimanual interference or coupling task with three right-hemisphere brain damaged stroke patients, with 10 healthy, age matched controls. During this task the participants are asked to draw lines with their right hand (intact hand for AHP patients) and to draw circles with their left hand (paralysed hand for AHP patients) while blindfolded. The lines drawn by the intact hand in AHP patients became more oval, clearly demonstrating that there was an intention to move the paralysed hand. Anatomically, all three AHP patients had lesions to the insula ribbon, which is inline with recent findings on the critical role of the insula in AHP (Berti et al., 2005; Karanath et al., 2005; Fotopoulou et al., 2010; Vocat et al., 2010). Garbarini and colleagues argue that both the insula and premotor areas provide the neural basis for the comparator component of the motor system. As we explain in the following sections, despite the prominence of this view, the multiple facets of AHP suggest that the syndrome cannot be sufficiently accounted for by a disruption of sensorimotor mechanisms.

1.6.2.2 Motivational account and affective processes

The role of emotion in anosognosia has long been described in the literature dating back to Banbinski when it was first described a century ago. Yet despite a long tradition of clinical descriptions and theoretical debates (Bisiach & Geminani, 1991; Weinstein & Kahn, 1955), issues surrounding emotion and motivation are only occasionally mentioned in the literature and have not received systematic empirical attention as potential

contributing factors (see Vuilleumier, 2004 for review). For example, milder forms of unawareness, such as anosodiaphoria, which is described as emotional indifference to hemiplegia, is a direct example of the relationship between awareness and emotional processes. Other emotional disturbances (often having varying clinical presentations) are also frequently reported in AHP patients, including inappropriate cheerfulness (Gainotti, 1972), but also apathy (Cutting, 1978). Additionally, differences found between implicit and explicit awareness (Fotopoulou et al., 2010; Cocchini et al., 2010; Moro et al., 2011) as well as fluctuations in awareness described in clinical case studies (Kaplan-Solms & Solms, 2000) are also not accounted for in modular theories of anosognosia. Therefore, it is important to consider that pure motor accounts for AHP do not explain the full range of clinical variability, including the less understood dynamic, emotional and delusional features (Fotopoulou, 2012).

Certain authors have therefore proposed that AHP should not only be explained by a disruption of sensorimotor mechanisms, but neuromotivational factors must also be considered (Fotopoulou, 2010; Turnbull, Fotopoulou, & Solms, 2014; Vuilleumier, 2004). There has been a long tradition of regarding anosognosia as a psychological defense, most importantly dating back to the work of Weinstein and Kahn (1955). This motivational account of anosognosia has been mostly set aside for its lack of emphasis on the associated brain regions involved and the lack of experimental data. However, there has been a recent shift to reinvestigate the role of emotional and motivational factors associated with AHP (Feinberg, 2007; Fotopoulou et al., 2010; Nardone, Ward, Fotopoulou, & Turnbull, 2007; Orfei et al., 2007; Turnbull et al., 2014; Vocat et al., 2010). With the emergence of an ‘affective neuroscience’ (see Panksepp, 1998)-emphasising the brain systems involved in basic human emotions in mammals- it is more widely recognised that ‘non-emotional’ processes, such as memory and attention, and emotional processes often overlap and can commonly involve the same neural mechanisms. Some authors (Fotopoulou, 2010; Turnbull et al., 2014; Turnbull & Solms, 2005) have therefore suggested that traditional motivational accounts of AHP could be modified to include a combination of factors, both neurocognitive and neuroemotional.

As the role of the right-hemisphere, particularly in the anterior insular cortex, for processing affective information (Craig, 2009; Damasio et al., 2000) and social cognition (Frith & Frith, 1999) is now increasingly recognised, there is scope for empirical investigations on the emotional and social underpinnings of AHP following right-

hemisphere lesions. Although it has been suggested by some authors that the right hemisphere is specialised for negative emotions (e.g. Davidson, 2001), and the subsequent loss of negative affect in AHP, it has been demonstrated by numerous studies that a range of emotions, both positive and negative, are experienced by these patients (Ramachandran, 1996; Kaplan-Solms & Solms, 2000; Turnbull et al., 2005). Descriptive case studies and experimental investigations have persistently shown that AHP patients experience a variety of emotions, but the incidences and diversity of emotional changes (i.e. emotion regulation) remains to be more fully explored (Turnbull et al., 2005). Even in the earliest reports of anosognosia, Babinski (1914) identified the relationship between unawareness and lack of emotional concern (anosodiaphoria). In Kaplan-Solms and Solms' (2000) case series, some patients presented with explicit dislike or hatred for their paraplegic arm (misoplegia), while others presented with a fluctuation of emotion including so-called 'catastrophic reactions' (sudden, intense episodes of tearfulness and emotional breakdown) that was followed by transient awareness of their deficit (also see Turnbull et al., 2002).

In response to these modular models of AHP, Vuilleumier (2004; also see Vocat et al., 2010; Vocat, Saj & Vuilleumier, 2013) has proposed a general "ABC model" of anosognosia. This model aims to account for the range in clinical variability in AHP. The ABC model proposes that there is a combination of deficits affecting at least three main processes: assessment, belief and control operations. When there is a faulty or broken interaction between these three processes it results in patients presenting with motor unawareness. In comparison, Fotopoulou (2012; 2014) has recently provided an alternative model to explain the multifaceted nature of anosognosia using a Bayesian 'predictive coding' framework (Friston, 2010). This framework allows for a single and neurobiologically plausible formulation that incorporates both bottom-up and top-down mechanisms of perception and belief formation. In this context, AHP can be linked to a general antagonism between 'prior beliefs' (predictive internal models of the world based on previous learning) and 'prediction error' (discrepancies between expected and actual inputs based on interoceptive and exteroceptive signals). Both of these models have tried to synthesize cognitive explanations together with emotional and delusional components of anosognosia. However, these more integrative accounts still fail to specify what the exact role of emotion in anosognosia is, and only provide an overarching theoretical model that allows for the inclusion of the emotional and delusional features of AHP.

Anosognosia has also been understood in the context of a loss of emotion regulation functions, which attempts to account for the many disregarded aspects of AHP, such as fluctuations of awareness overtime, variations in clinical presentation and implicit awareness (Turnbull et al., 2014). Turnbull and colleagues propose that the relationship between the rightward lateralisation of disorders of awareness and emotional experiences is not as a result of abnormalities in emotional processing in general, but rather attributed specifically to a deficit in the ability to regulate emotions. Emotion regulation has been increasingly shown to be a right-lateralised psychological function (Nardone et al., 2007), with neuroimaging (Chambers, Garavan, & Bellgrove, 2009) and lesion studies (Salas, Gross, Rafal, Viñas-Guasch, & Turnbull, 2013; Salas, Gross, & Turnbull, 2014) confirming this hypothesis. Although no empirical studies have yet validated this model, it is proposed that damage to the right-lateralised emotion regulation system causes motor unawareness in AHP by making the patient revert to early developmental responses, such as denial (Turnbull et al., 2014).

In summary, although many cognitive theories have been proposed to explain AHP, no single model has been able to account for its multifaceted and heterogeneous nature. Furthermore, as argued above, cognitive, modular models, and even more integrative accounts have failed to adequately address the role of emotion in anosognosia. Affective factors have in most cases been too quickly disregarded and there have been no experimental studies directly investigated the role of emotion in motor unawareness. There is a need for future studies to further explore the relationship between emotion, both positive and negative, and unawareness of deficit. Given that in other domains patients' emotions and motivation can have a significant role in any rehabilitation effort, the relationship between awareness recovery and mood can also be studied, potentially providing valuable insight into effective rehabilitation strategies of these patients. This will be one of the aims of this thesis, as explained below.

1.6.2.3 A proposed social account for AHP

It has been tentatively proposed that there is a unique relationship between 'spatial' aspects of anosognosia and affective factors (Kaplan-Solms & Solms, 2000; Turnbull et al., 2014). Importantly, right-hemisphere damage is more frequently associated with disorders in spatial cognition (Maguire et al., 1998; Kaplan-Solms & Solms, 2000). Some experimental evidence has demonstrated that manipulating patient's spatial perspectives, by showing them a 3rd person (other) viewpoint using mirrors, can temporarily affect their

ability to perceive their motor deficits (Fotopoulou et al., 2011). As explained in more detail below, video replay that also draws on spatial 3rd person perspective taking permanently reinstated motor awareness in a single-case study investigation (Fotopoulou et al., 2009). Turnbull et al. (2014) suggest that AHP patients, as a consequence of their right-hemisphere damage, are more inclined to perceive the world subjectively (from a 1st person perspective) rather than objectively (from a 3rd person perspective). Selective studies have further shown that there are differences in awareness depending on if the questions were self referent or other referent (e.g. referring to the paralysis of another person; Marcel et al., 2004; Moro et al., 2011). Similarly, recent experimental evidence has suggested that affective processes in AHP are more pertinent in relation to the self than to others (Turnbull et al., 2005). Clinical reports and experimental findings have therefore posed the question of the role of perspective taking (both visual and verbal) in anosognosia.

This concept of perspective-taking has frequently been explored under the generic concept of ‘mentalisation’ or ‘Theory of mind’ (ToM). This unique ability is most frequently conceptualised as the ability to infer the thoughts and feelings of others (Premack & Wooclyff, 1978), and most broadly, as the ability to take another person’s perspective (Frith & Frith, 2007; Hynes, Baird & Grafton, 2006). Furthermore, perspective taking involves both the ability to mentally adopt someone else’s perspective and visual-spatial perspective taking that necessitates the ‘mental rotation of the self in space’ (Kessler & Thomson, 2010, pp.73). Kessler and Thomas propose that this rotation of the self in visual-spatial perspective taking is grounded in internal representations of the body that require adopting other viewpoints (i.e. other bodies). Within this framework, self- or 1st person perspective taking is centered around one’s own body, while other- or 3rd person perspective taking allows us to take the vantage point of someone else (Vogeley et al., 2004; Vogeley & Fink, 2003).

Several lesion studies have also provided consistent anatomical evidence that ToM processes, at least in part, rely on right-hemisphere functioning (Brownell, Griffin, Winner, Friedman & Happé, 2000; Griffin et al., 2006; Happé, Brownell, & Winner, 1999). Similarly, as described above, AHP is also most frequently associated with right-hemisphere damage. Although the neural mechanisms underlying social cognition and their related functions are not yet fully understood, neuroimaging and lesion studies have identified a network of functionally related, core brain regions, sometimes referred to as

the “mentalising network” (Aichhorn et al., 2009; Gallagher & Frith, 2003; Koster-Hale & Saxe, 2013; Siegal & Varley, 2002). Some of these areas have similarly been associated with AHP, such as the right temporal-parietal junction (TPJ; Vocat et al., 2010) and the right inferior and middle frontal gyri (Berti et al., 2005).

Unawareness of illness or lack of insight in patients with schizophrenia has also been thought to co-occur with impairments in ToM (Langdon & Ward, 2009). Here it is argued that awareness of illness in schizophrenia may depend on the ability to adopt the mental state of others. Using classic ToM tasks, Langdon and Ward (2009) suggest that impairments in the ability to take on another person’s perspective might compromise the patient’s ability to evaluate the reality of their own situation.

Overall, clinical case studies, results and interpretations of experimental findings and lesion evidence all suggest a possible role of social processes in contributing to the presentation of anosognosia. However, no study has directly investigated the relationship between perspective taking (as an underlining modality of social cognition) and self-awareness through the study AHP. Specific studies are therefore needed to examine the relationship between spatial cognition, social cognition and AHP. This will be one of the aims of the present study as outlined below.

1.7 Awareness recovery and interventions

Anosognosia is often a transient phenomenon, not frequently lasting beyond the acute stage. AHP typically spontaneously recovers within days, weeks or months from onset. However, unawareness of illness, especially in early critical stages, may significantly obstruct rehabilitation efforts (Gialanella, Monguzzi, Santoro & Rochi, 2005; Jehkonen, Laihosalo, & Kettunen, 2006). For example, anosognosia is said to be associated with longer hospital admissions (Maeshima, Dohi, & Funahashi, 1997) and poor functional recovery (Gialanella et al., 2005). Additionally, systematic reviews of the literature suggest that approximately 30% of AHP patients remain unaware beyond the acute stage (Orfei et al., 2007; Pia et al., 2004). Recently some progress has been made in the management and rehabilitation of AHP (Prigatano & Morrene-Stupinsky, 2010; Jenkinson et al., 2011), but there is still no evidence-based treatment for AHP (Kortte & Hillis, 2011).

There has been a long tradition in using vestibular stimulation to initiate a remission of AHP, but unfortunately the results are only temporary (Cappa, Sterzi, Vallar, & Bisiach, 1987). Beschin, Cocchini, Della Sala, & Allen (2012) tested the effect of three types of treatment (optokinetic stimulation, prism adaptation and transcutaneous electrical nerve stimulation) on both neglect and anosognosia in five patients with severe AHP and neglect. A transient improvement of awareness was found in one patient using the combination of methods, and a temporary improvement of neglect found in two other patients using the same methods. However, these recent efforts only resulted in a temporary remission of AHP, similarly to vestibular stimulation.

A recent single case study investigation reported the first clinical intervention to successfully lead to an immediate and permanent remission of AHP for the first time in the literature (Fotopoulou et al., 2009). Fotopoulou and colleagues used video replay as an experimental rehabilitation intervention method. Self observation in video replay offers a unique visual perspective by showing the patient both a 3rd person (from the outside) and ‘offline’ (watching oneself at a later time than the actual attempt to execute a movement) perspective. Video replay was used to provide visual feedback to a patient with severe AHP. Below a brief vignette of the published case study is presented in order to illustrate the main elements of this approach.

Case example

LM was a 76-year-old right handed women with 15 years of education. She had no significant previous medical or psychiatric history, and was hospitalised following a right middle cerebral artery (MCA) stroke. She presented with severe left-sided hemiplegia (0/5 power on Medical Research Council scale), mild dysarthria, facial weakness, proprioception deficits and hemispatial and personal neglect. Neuropsychological testing further reported mild executive impairment and anxiety, but no indications of depression. LM had severe AHP, as supported by her scores on both the Berti interview (Berti et al., 1996) and Feinberg Questionnaire (Feinberg et al., 2010). She further claimed that she could perform a number of bimanual and bipedal tasks (e.g. walking and clapping hands), and spontaneously reported false memories of such actions, including walking around the ward and washing and dressing herself without assistance. (Fotopoulou, Rudd, Holms & Kopelman, 2009).

Patients with AHP typically remain anosognosic when their paralysed arm is brought to their ipsilateral (i.e. on the same side of their body) visual field. In contrast, a 90s video clip of LM answering awareness questions was played back to her, therefore providing video-based feedback to the patient. As a result the authors noted an immediate and spontaneous increase in motor awareness post-video intervention. LM's awareness recovery was additionally maintained at a one-month (four week) follow-up. One important interpretation from the authors is that AHP patients may have more intact awareness when observing themselves from a 3rd rather than a 1st person perspective. A second interpretation is that there are functional and neural differences between 1st and 3rd person perspectives on the body, and this allows us to differentiate our body from other peoples. Interestingly, since video-viewing also provides the patient with an "offline" perspective (i.e. they are not trying to move their arm while watching the video), the impact of motor intentions is not relevant to motor monitoring during video observation. Video-viewing may have therefore facilitated the updating of LM's motor awareness (i.e. 3rd person and off-line self observation, using video replay, facilitated 1st person body awareness). These results however need to be replicated and the precise mechanisms of this effect, as well as other therapeutic factors that should potentially accompany the intervention (e.g. emotional support), need to be specified.

Video replay has also been shown to help improve insight of psychotic patients (Davidoff, Forester, Ghaemi & Bodkin, 1998). In a more recent study, David, Ster, & Zavarei (2012) measured the effect of "self" and "other" video replay on insight of psychosis with a group of 40 schizophrenic patients. Twenty-one patients watched the "self" referent video and 19 patients watched the "other" referent video (an actor presenting with the same psychotic symptoms). Both videos resulted in an improvement of insight. Although there was a lack of a clear difference in the effect of the self and other video replay, patient's insight did appeared to improve more after viewing themselves and/or the other patient in the video.

Future studies are needed to further test the feasibility of self-observation using video replay. Firstly, there is a need to test this video intervention with both acute and chronic patients, in order to test whether spontaneous recovery can account for remission of AHP in the initial case study (Fotopoulou et al., 2009) with an acute stroke patient. Additional components for the optimisation of the rehabilitation intervention also deserve further investigation, for example: the use of emotional support and therapeutic strategies; testing

the *extension* (see Section 1.3 of this Chapter) of remission of unawareness symptoms after using video replay, such as admitting to failures to move left arm and leg as well as realistic estimates of the functional significance of their paralysis; the use of a standardised protocol; and to explore how individual differences effect the administration of such direct rehabilitation interventions. Therefore, future studies are needed to first test the feasibility and effectiveness of the video replay intervention, followed by larger group studies and clinical trials. These were the aims of a clinical, rehabilitation case series study, presented in Chapter 6.

1.8 Study rational and chapter overview

In light of the above, considerable empirical evidence supports the idea that AHP involves a breakdown in motor planning and monitoring (Fotopoulou et al., 2008; Jenkinson, Edelstyn, Drakeford & Ellis, 2009; Garbarini et al., 2012). However, as argued above, purely motor accounts do not explain several features of the phenomena, such as emotional and delusional elements (Fotopoulou, 2012; Kaplan-Solms & Solms, 2000). Accordingly, this thesis argues that a revision of the prevailing, modular theories of AHP is necessary, taking into consideration the involvement of (i) emotion and motivation, and (ii) social mentalising and perspective taking. These findings on the role of emotion and social processes in AHP can then be translated and used in future rehabilitation strategies for AHP. Therefore this thesis will argue in favour of a new account of unawareness following right-hemisphere stroke, predicting that AHP patients live in an emotionally-laden, egocentric reality, where the ability to adopt a 3rd person perspective or the link between 1st and 3rd person thinking is defective.

The current thesis aims to advance our understanding of the neurocognitive, emotional and social factors involved in anosognosia. Recent advances in AHP research can be attributed to a number of interrelated factors discussed in detail above (Fotopoulou et al., 2012), such as: improvements in neuroimaging methods that have allowed for the exploration of the anatomical correlates of AHP; and the use of well-controlled, psychophysiological experiments that supplement standardised neuropsychological assessments. Therefore the current study will draw on an integrative methodological approach, using neuropsychological testing, psychophysiological experiments and neuroimaging methods.

Accordingly, the series of experimental investigations in this thesis aims to set the foundation for further, clinically oriented research on AHP, as a prototypical form of unawareness. In particular this thesis aims to: (1) investigate the emotional and social factors, that underlie motor unawareness in stroke patients; (2) identify the neurocognitive factors and neural (neuroanatomical) correlates that underlie motor unawareness; and (3) develop potential bedside, rehabilitation interventions for AHP. The proposed PhD will focus on these related research topics of interdisciplinary scope with the intention of improving our psychological, neuropsychological and neuroscientific understanding of AHP. Accordingly, the main research question guiding this thesis is:

What are the emotional and social factors, and their neural counterparts, that underlie motor unawareness in stroke patients, and what is their relationship with the associated neurocognitive factors?

A secondary research question being:

How can we translate emotional and social experimental and neuroimaging findings to design and implement therapeutic bedside studies and appropriate interventions for motor unawareness post stroke?

More specifically the aims of the present series of experiments was too:

1. Experimentally investigate the influence of positive and negative emotion on unawareness. (Chapter 3)
2. Experimentally investigate the relationship between social cognition and AHP, under the broad theoretical framework of ToM, specifically looking at 1st and 3rd person perspective taking. (Chapter 4)
3. Experimentally investigate under what conditions motor awareness changes (i.e. partiality of motor awareness, Chapter 5), specifically examining:
 - a. Differences in 1st versus 3rd person perspective taking.
 - b. If motor awareness extends to the motor deficits of other paralysed patients.
 - c. Differences in severity of motor awareness for the self and ‘other’ patient.

4. Investigate the neurocognitive factors and neuroanatomical correlates that underlie motor unawareness by using neuropsychological testing and lesion analysis methods, to develop a clearer understanding of the neural basis of anosognosia. (Chapters 3-5)
5. Design and experimentally investigate bedside, therapeutic studies for the rehabilitation interventions for AHP. (Chapter 6)

1.8.1 Summary of experimental chapters

The following chapters describe a series of experimental and case study investigations carried out in order to address each of the above aims. Chapter 2 provides a general overview of the methods used in this thesis, combining neuropsychological testing, psychophysiological experiments and neuroimaging methods. The chapter will explain details of patient inclusion and recruitment, and ethical approval. Neuropsychological and neurological tests used during patient assessments will be described, as well as detailing the neuroimaging methods used to analyse clinically acquired CT and/or MRI scans for lesion overlay, subtraction, and VLSM analysis. Detailed experimental methods and statistical analysis used for each experiment will be specified in each individual chapter, and are therefore not included in the general methodological overview provided in Chapter 2.

In Chapter 3 the possible role of emotion in AHP is experimentally investigated. The study aimed to investigate how positive and negative emotions influence motor awareness in anosognosia. Positive and negative emotions were induced under carefully-controlled experimental conditions in right-hemisphere stroke patients with AHP ($n = 11$) and controls with clinically normal awareness ($n = 10$). Using lesion overlay and VLSM approaches, the brain lesions associated with the diagnosis of AHP, as well as performance on the experimental task is explored.

The relationship between social cognition and self-awareness is experimentally investigated in a series of studies in Chapter 4. Two experimental studies were used to examine the role of visual-spatial perspective taking and ToM, comparing 1st person perspective taking and 3rd person perspective taking abilities in patients with AHP ($n = 15$) and HP controls patients ($n = 15$), as well as age-matched healthy (non-neurological) control participants. Furthermore, using lesion-mapping methods, the areas commonly damaged in neurological patients with and without AHP were identified and VLSM

analysis was used to investigate the relationship of the damaged brain areas to the behavioural scores in the experimental tasks.

In Chapter 5 self-other processes in motor awareness was explored in relation to *partiality* of awareness. Three experimental studies were conducted with 38 right-hemisphere damaged patients (AHP: n = 19; HP: n = 19) to examine under what conditions motor unawareness changes. These studies explored whether 1st and 3rd person verbal perspective taking changes motor unawareness for the self and of another paralysed patient. A second aim being to test if motor awareness extends or generalises to include the motor deficits of other paralysed patients and if there is a difference in the severity of unawareness for the self and the other patient. Lastly, the potential difference between self referent and other referent awareness is examined using disability related ToM stories. Lesion mapping methods (i.e. lesion overlay and VLSM) were used to identify the difference in lesioned areas in AHP compared to HP patients, and investigate the relationship between self-and-other referent differences and related brain areas.

A case-study approach is used to explore possible rehabilitation interventions for AHP in Chapter 6. The study is based on the recent, bedside intervention, namely self-observation by video replay. This procedure has been adjusted and applied, as the basis of two intervention protocols administered to two patients with severe AHP. The first study used multiple, successive sessions of video-based self-observation in an acute patient, targeting first the awareness of upper limb and subsequently lower limb paralysis. The second study used a single session of video-based, self-and-other referent observation in a patient at the chronic stage following onset. Both protocols also involved elements of rapport building and emotional support.

Lastly, a general discussion of the findings in relation to the main research questions guiding this thesis is presented. Results are discussed in the context of current theoretical perspectives, methodological issues and limitations are examined, applications to future rehabilitation strategies are proposed, and an outline for future research concludes this thesis in Chapter 7.

Chapter 2 General Methods

The purpose of this chapter is to provide a general overview of the methods used in this study, as well as information regarding participant inclusion and recruitment, and ethical approval. The methods described here are the ones shared between the subsequent chapters that focus on individual experiments and related methodological issues.

2.1 Participants

Patients fitting the following inclusion criteria were eligible to take part in this study. The main sample for this study consisted of acute neurological (i.e. stroke) patients, with clinically defined right-hemisphere damage and left-sided weakness (see below for detailed inclusion criteria). Stroke patients were classified as having anosognosia for hemiplegia (AHP) using the awareness assessments specified below and subsequently assigned into the experimental group (AHP group) and hemiplegic control group (HP group). In specific experiments, an additional control group of age-matched healthy (i.e. non-neurological) volunteers were recruited.

2.1.1 Target group

The target or experimental group of this study consisted of adult neurological (stroke) patients with right-hemisphere lesions and contralateral hemiplegia. All patients presented with clinical indications of AHP, which were formally tested using awareness assessments specified in Section 2.3.1 of this Chapter. The inclusion and exclusion criteria are specified below.

Inclusion criteria

1. Clinical indications of anosognosia for hemiplegia: quantified by formal testing during this study.
2. Right-hemisphere damage, as detected by CT and/or MRI investigations and confirmed by neurological and neuropsychological assessments (e.g. left-sided motor weakness; presence of neglect).
3. Recent pathology: patients were recruited less than four months post symptom onset (acute to sub-acute stage post-stroke).
4. Contralateral hemiplegia, or other left-sided motor impairment: standard neurological testing confirmed presence and severity of motor deficit.

Exclusion Criteria

1. Generalised brain damage.
2. Previous neurological or psychiatric history.
3. Less than seven years of education.
4. Acute confessional state: forward digit span less than 4, abnormal sleep-wake cycles.
5. Dementia: as reported in medical records.
6. Severe impairments in language: unsatisfactory comprehension, expression or communication.

2.1.2 Control groups

2.1.2.1 Neurological controls

The main neurological control group consisted of adult neurological (stroke) patients with right-hemisphere lesions and contralateral hemiplegia. No patients presented with clinical indications of AHP, which were formally tested using awareness assessments specified in Section 2.3.1 of this chapter. The inclusion and exclusion criteria are specified below. The only difference between the experimental group and neurological control group was a clinical diagnosis of AHP.

Inclusion criteria

1. Right-hemisphere damage, as detected by CT and or MRI investigations and confirmed by neurological and neuropsychological assessments (e.g. left-sided motor weakness; presence of neglect).
2. Recent pathology: patients were recruited less than four months post symptom onset.
3. Contralateral hemiplegia, or other left-sided motor impairment: standard neurological testing confirmed presence and severity of motor deficit.

Exclusion Criteria

1. Clinical indications of anosognosia for hemiplegia: quantified by formal testing during this study.
2. Generalised brain damage.
3. Previous neurological or psychiatric history.
4. Less than seven years of education.

5. Acute confessional state: forward digit span less than 4, abnormal sleep-wake cycles.
6. Dementia: as reported in medical records.
7. Severe impairments in language: unsatisfactory comprehension, expression or communication.

2.1.2.2 Healthy controls

An additional control group of healthy volunteers (non-neurological controls) were also used for specific studies. Relevant exclusion criteria are specified below.

Exclusion criteria

1. Previous neurological or psychiatric history.
2. Motor paralysis, motor weakness or any other related impairment.
3. On medication with severe cognitive or mood effects.
4. Less than seven years of education.
5. Severe impairments in language: unsatisfactory comprehension, expression or communication.

2.2 Patient identification, recruitment and ethics

2.2.1 Patient identification and recruitment sites

This thesis fell part of a split-site collaboration project between the United Kingdom and South Africa, specifically between the University of Cape Town, and King's College London and University College London. Accordingly patient recruitment took place at South London Hospital sites. Patients were identified and recruited from consecutive admissions to acute stroke wards from three hospital sites in the United Kingdom (UK), specifically: Mark Ward at St Thomas' Hospital; The Friends Stroke Unit at Kings College Hospital; and William Drummond Ward and Brodie Ward at St George's Hospital. For selective studies, patients were additionally recruited from a collaborating hospital site in Italy, namely: the Rehabilitation Unit of the Sacro Curora Hospital in Negrar, Verona. Healthy, non-neurological, volunteers were recruited from St Thomas' Hospital among the visitors to the hospital wards. Recruitment took place over approximately a two-year period from September 2012 to April 2014. Patients recruited from the partnered Italian hospital site were a consecutive series of patients meeting full inclusion criteria. The general discussion in Chapter 7 (see Section 7.4) provides a

detailed discussion of potential limitations involved in recruiting from multiple hospital sites and testing in different languages.

2.2.2 Ethics approval

This study was granted a favourable opinion by the National Research Ethics Service (NRES) in the UK. Research and Development (R&D) approval was individually sought and granted for each participating site. The investigator held honorary contracts with all recruitment sites involved in the UK. Furthermore, the investigator carried out numerous presentations to the staff at the various hospital sites and liaised regularly with the responsible clinical staff regarding the progress of the study. This study was additionally approved by the local ethics committee in Italy, our collaborating research site, and carried out in accordance with the guidelines of the Declaration of Helsinki.

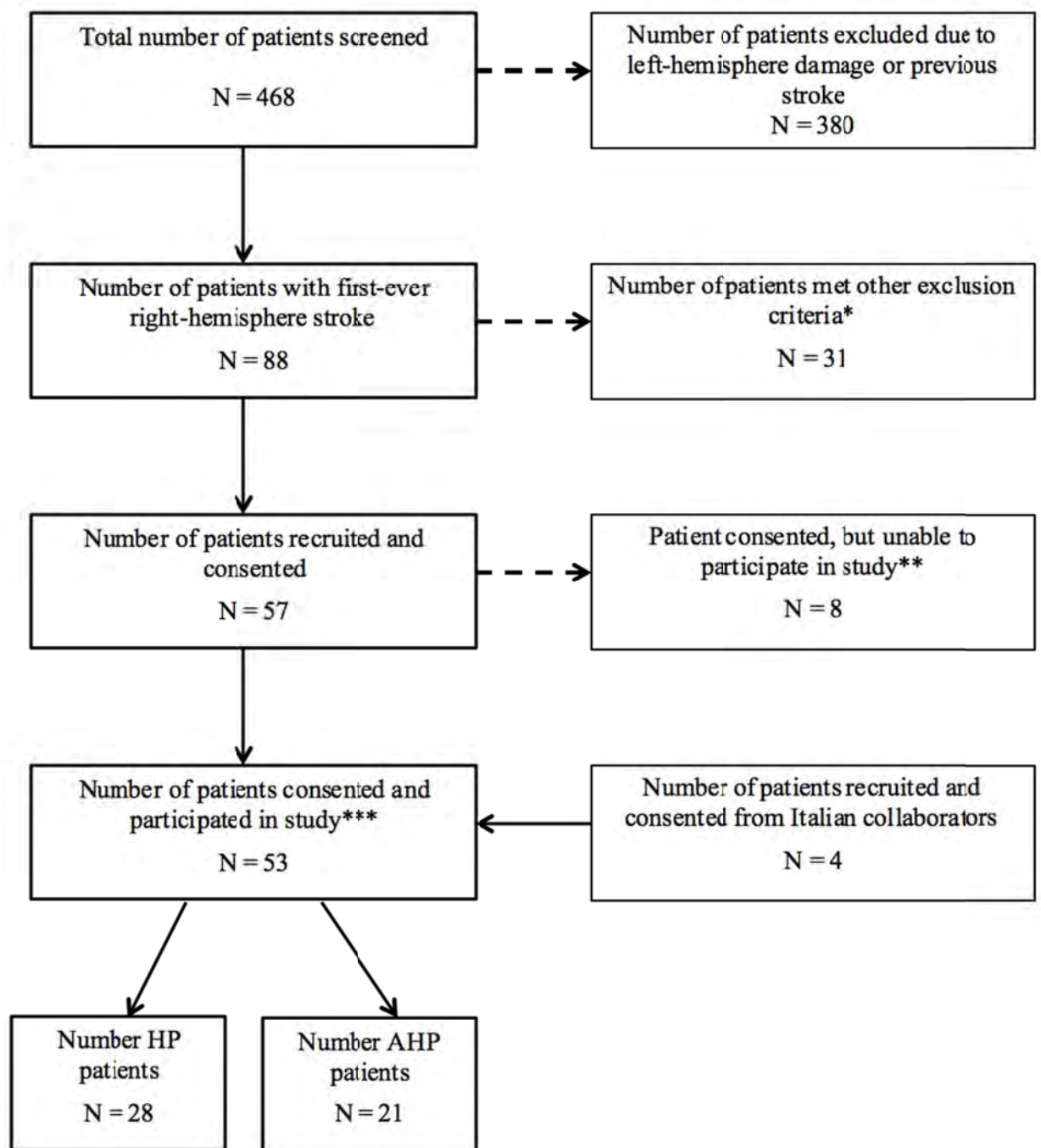
2.2.3 Process of consent and recruitment procedures

Patients were all approached under the guidance of the clinical team at the hospital sites and informed written consent was obtained for each participant. After the purpose of the study was explained to the participants, there were asked if they wished to participate in the study. They were informed that their participation is entirely voluntary and that they can withdraw from the study at any time, without consequences and without giving a reason. If the participant was in favour of participating in the study, the researcher then carefully read through the information sheet and consent forms, at the pace appropriate for the participant, especially for the patient populations. The participants were encouraged to ask questions and discuss the study. If the participant agreed to take part in the study, he or she was asked to sign the consent form. It was emphasised, that the participants did not have to make a decision immediately and that they could do so within a three-day period. A copy of the Information Sheet(s) and Consent Form for patients and healthy participants is in Appendix A and B.

Stroke patients were all tested at the bedside in their allocated rooms on the hospital ward. The number and time of testing sessions varied between patients, depending on: time availability between clinical appointments; general fatigue and mood; or if patients were medically well to participate. Therefore, in general, testing took between five to ten sessions to complete, with each session lasting a maximum of one hour. When possible, testing sessions were performed on sequential days until all assessments had been completed in the shortest possible time frame.

A summary of patients screened and recruited is presented in Figure 2.1. The data pertains to: (i) the total number of patients screened; (ii) the number of patients excluded; (iii) patients consented and recruited, but unable to participate in study due to medical complications, severe fatigue, hospital transfer or death; (iv) the total number of patients consented and participating in the study; and (v) the total number of AHP and HP control patients. The number of patients contributing to each individual experiment, as well as demographic and clinical characteristics, are detailed in each chapter separately.

Figure 2.1 *Summary of stroke patients identified, recruited and tested*



*Other exclusion criteria included: other neurological conditions, such as dementia; psychiatric history; confusion and /or disorientation; and/or motor strength too great.

**Patients were unable to participate due to medical complications, being transferred to other hospitals, severe fatigue and/or unexpected death.

***This number is including the patients identified and tested by the Italian collaborators; patients participated in pilot and experiments studies.

2.3 Integrative methodological approach

This study uses a combination of methods in order to investigate the emotional and social processes and neural biases of anosognosia. This integrative methodological approach is used in the group studies in the subsequent chapters. The methods used include: (i) clinical and neuropsychological assessments; (2) well-controlled, psychophysiological experiments (see Jenkinson & Fotopoulou, 2010 and Fotopoulou, 2012 for discussion); and (3) structural neuroimaging methods, software and statistics for lesion mapping that identified brain lesions selectively associated with AHP and other experimental measures. The clinical and neuropsychological assessments, as well as the neuroimaging methods used, are detailed below. However, the experimental design, methods and statistical analysis used in the psychophysiological experiments are specified in each chapter separately.

2.3.1 Anosognosia assessments and classification of AHP patients

As discussed previously in Chapter 1, there is no gold standard assessment for AHP. Patients were therefore classified as having AHP using two assessment measures: the Berti interview (Berti et al., 1996) and the Feinberg Scale (Feinberg et al., 2010). The Berti interview was the basis of the classification of patients with AHP, and the Feinberg scale used to specify the severity of the anosognosia.

The Berti interview

Classification was firstly based on the Berti verbal awareness interview (Berti et al., 1996). The interview began with general questions (e.g. ‘Why are you in the hospital?’), then followed by specific questions regarding motor ability (e.g. ‘Can you move your left arm?’), and ‘confrontation’ questions (e.g. ‘Please touch my hand with your left hand. Have you done it?’). The structured interview is scored on a three-point scale: 2 = denial of motor impairment and failure to reach the examiners hand (severe anosognosia); 1 = denial of motor impairment, but admits to failure to reach examiner hand (mild anosognosia); and 0 = full acknowledgment of motor deficits (normal). Patients scoring one or two were categorised as anosognosic.

The Feinberg awareness scale

The Feinberg et al. (2000) scale was used as a secondary measure of unawareness to rate the severity of the anosognosia. The scale consists of 10-items (see Appendix C). Questions begin with general self-report items (e.g. ‘Do you have any weakness

anywhere?’), followed by emotion related items (e.g., ‘Are you fearful about losing your ability to use your arm?’) and items asked from a 3rd person perspective (e.g., ‘The doctors tell me that there is some paralysis in your arm. Do you agree?’). The questions conclude with task-related and ‘confrontation’ items (e.g. ‘Please try and move your left arm for me. Did you move it?’). Responses were scored by the examiner for each item: 0 = no awareness; 0.5 = partial unawareness; and 1 = complete unawareness. The responses are summed to produce a composite ‘Feinberg awareness score’: 0 = complete awareness, 10 = complete unawareness.

2.3.2 Neurological and neuropsychological assessment

In addition to the above awareness assessments, all patients underwent neurological and neuropsychological assessments. As patients were in the acute stage following stroke and were routinely tested at the bedside, all tests were chosen and tailored to be suitable for bedside assessments. Detailed descriptions of the neurological and neuropsychological tests used are specified below. During testing sessions patients were also asked relevant demographic (e.g. years of education, employment) and medical information using routine history taking procedures. Other relevant demographic or medical information (e.g. date of birth; date of onset; radiology report) was acquired in the patients’ medical folders, under supervision of the clinical team (please see Appendix D). Qualitative or clinical observations regarding the behaviour of participants during assessments were also made. These behavioural observations were not documented in a systematic manner during time of testing, but were still useful in reflecting on the individual differences and quantitative results. These results are reported where appropriate in the subsequent chapters.

Motor strength

Motor strength of the upper and lower limbs was assessed using the Medical Research Council scale (MRC; Guarantors of Brain, 1986). The extent of motor impairment can vary from complete flaccidity (MRC score 0) to slight movements (MRC score 1–2). The MRC scale grades motor power on an ordinal scale: 0 = no contraction; 1 = flicker or trace of contraction; 2 = action movement, with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; 5 = normal power.

General cognitive functioning

The Wechsler Test of Adult Reading (Wechsler, 2001) was used to provide an estimate of premorbid intellectual function. The test operates on a basis that vocabulary correlates highly with education and IQ and that verbal skills, such as reading ability, remain intact even in cognitively deteriorating patients. The tests comprises of a list of 50, phonetically irregular words. As the correct pronunciation of each word cannot be determined from it's spelling, it is argued that the test relies on prior knowledge rather than current cognitive capacity. Participants are asked to read aloud a list of words, which are scored for pronunciation errors by the examiner. The test was used in the present study to compare the IQ of AHP and HP patients, as well as age matched healthy volunteers.

Orientation in time, space and person, as well as general cognitive functioning, was assessed using the Montreal Cognitive Assessment (MOCA; Nasreddine, 2005). The MOCA was chosen in order to exclude patients from the study who were in a confusional state or had severe generalised cognitive impairment. It is a brief screening test used to measure the severity of confusion or cognitive decline. It provides a general overview of several cognitive domains, including: orientation (to time and place), attention, memory, dysphasia, apraxia and executive function.

Memory tests

Working memory was assessed using the digit span task, forwards and backwards, from the Wechsler Adult Intelligence Scale III (WAIS III; Wechsler, 1997). Long-term verbal recall was also specifically assessed using the five-item test from the MOCA. Patients are asked to remember five items and are tested on immediate recall, with category clues and multiple-choice options are given when needed. The five items are then repeated, with immediate recall tested again. Finally, delayed recall is tested on the five items. Category clues and multiple-choice options were provided if necessary, however points are only given for uncued recall items.

Neglect tests

The Behavioural Inattention Test (BIT; Wilson, Cockborn & Halligan, 1987) is a standardised test used to assess unilateral visual-spatial neglect commonly occurring after right-hemisphere damage. Five of the conventional subtests from the BIT were administered: line crossing, star cancellation, copy, representational drawing and line bisection.

Personal neglect was assessed using the ‘one item test’ (Bisiach, Vallar, Perani, Papani & Berti, 1986), and a more sensitive measure, the ‘comb/razor’ test (Mcintosh, Brodie, Beschin, & Robertson, 2000). The one item test is a routine clinical test in which the patient is asked to use their right hand (ipsilateral side) with their left hand (contralateral side). The patients movement or attempt to move is rated on a three-point scale: 0 = good; 1 = done but with small error, uncertainty or latency; 2 = the search is interrupted before the search is completed; and 3 = no movement towards the other hand is performed. The Comb and Razor Test is a measure of unilateral spatial neglect in the patient’s personal space (called personal neglect) by assessing their performance in functional activities, such as using a comb or a razor. The percentage bias of the total score is calculated using the following formula: $\%bias = (left - right\ strokes) / (left + right + ambiguous\ strokes)$. The ‘%bias’ formula yields a score between -1 (total left neglect) and +1 (total right neglect). The cut off for left personal neglect is $\% bias < -0.11$.

Tests of executive functioning

Executive and reasoning abilities were assessed using the Frontal Assessment Battery (FAB; Dubois et al., 2000), and the Cognitive Estimates test (Shallice & Evans, 1978).

The cognitive estimates test was used to measure the ability to make complex mental calculations and estimations. The FAB consists of six subtests: similarities and abstract reasoning; mental flexibility; motor programming and executive control (Luria motor sequence); conflicting instructions; inhibitory control (go-no-go test); and precision behaviour. Each subtest has a maximum score of three (the higher the better), and a total score of 18 is generated.

Emotion-related tests

The Hospital Depression and Anxiety Scale (HADS; Zigmond & Snaith, 1983), was used to assess depression and anxiety. This is a self-rating scale used for measuring levels of anxiety and depression. The test is specifically designed to be used with patients with physical difficulties, so that symptoms such as fatigue do not raise the depressed mood score. A raw total score of eight or higher on the depression or anxiety subgroups indicated the presence of clinical depression and/or anxiety.

Clinical tests

Proprioception was assessed with a clinical protocol based on Vocat et al.’s (2010) procedure. The patient’s eyes are closed throughout the assessment, with small, vertical

and controlled movements applied to three joints (middle finger, wrist and elbow), at three time intervals. Correct responses were rated as zero and incorrect ones as one (Vocat et al., 2010; see Appendix E). The customary ‘confrontation’ technique was administered to test visual fields and tactile extinction (Bisiach et al., 1986). A clinical protocol was used to test disorientation for right and left. The patient is asked to identify their own right or left arm and leg, and use either their right or left arm to identify various body parts (e.g. right ear or left shoulder). The patient is also asked to identify the assessor’s right or left arm and body parts (e.g. right or left ear; see Appendix F).

2.3.3 Experimental methods

Experimental design, methods and procedures are described in full detail in each of the subsequent Methods Sections in the succeeding chapters.

2.3.4 Neuroimaging methods

Data acquisition

Neuroimaging was performed on all patients as part of their standard clinical treatment within the first week of admission to the Accident and Emergency (A&E) departments (admission to neuroimaging interval: mean = 4.26 days, SD = 4.88 days). These routinely acquired clinical CT images were obtained for all patients of this study. Some patients underwent additional magnetic resonance imaging (MRI) as part of their clinical diagnostics. Where available these MR images were used to cross-reference lesion location. All clinical images used for this study had been anonymised.

Neuroimaging pre-processing and processing

Available structural data were converted into software-readable formats for further processing. Accordingly, all images were pre-processed for visualisation using the dcm2nii programme (<http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html>). Visual inspection of the obtained files was performed in fslview (<http://fsl.fmrib.ox.ac.uk/fsl/fslview/>) to identify possible equipment-induced or patient-induced (e.g. movement) artefacts.

Lesion delineation

To facilitate comparison between the clinical data and a standard space template, the native structural scan of each patient were manually reoriented to the origin of the

template using SPM (Statistical Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm/>). The order of the patients was randomised. For each patient the structural scan was examined and anatomical landmarks were identified to acknowledge lesion location. Lesions were then reconstructed from available scans onto axial slices of the standard template provided within MRIcron (<http://www.mccauslandcenter.sc.edu/mricro/mricron/>). Other available imaging modalities were used for guidance where available. The corresponding binary mask was created for each lesion. An anatomist, who was blinded to the clinical information, groupings and study hypotheses, reviewed the reconstructions for accuracy and suggested corrections where necessary.

Lesion overlay and voxel-based lesion-symptom mapping

Lesion volume was extracted using FSL (FMRIB Software Library, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) and an independent sample t-test was used to identify mean differences between the two clinically defined groups (AHP vs. HP). To identify the areas that were commonly damaged within the sample of patients with and without AHP a lesion analysis was performed. Percentage lesion overlay maps for both groups and a subtraction map between them were computed in MRIcron.

To identify voxels within the brain that have a significant effect on behaviours, a voxel-based lesion-symptom mapping (VLSM) approach was implemented (Bates et al., 2003; Rorden, Karnath, & Bonilha, 2007). This advanced method characterises the statistical relationship between tissue damage and behaviour on a voxel-by-voxel basis, regardless of the classification of patients into categorical groups, or implementing a cut-off for pathology (Bates et al., 2003). This advanced lesion analysis was performed as linear regression analysis with the non-parametric mapping programme (NPM; <http://www.cabiatl.com/mricro/npm/>; Rorden & Karnath, 2004) and a VLSM mapping tool implemented in mricron, a method less sensitive to outlier profiles compared to other software packages (Rorden et al., 2007).

Experimental scores used for each VLSM analysis are specified in the subsequent chapters. Results were calculated with the permuted (number of permutations set to 1000) Brunner-Menzel test to correct for multiple comparison and small sample size (Rorden et al., 2007). Results were then projected onto a high-resolution template

(Holmes et al., 1998) in standard space. Anatomical locations were cross-referenced using the Juelich histological atlas (Eickhoff et al., 2007) implemented within FSL.

2.3.5 Summary and conclusion

The aim of this chapter was to provide an overview of the general methods used that span more than one experiment, in order to prevent repetition in subsequent chapters. The chapters to follow will provide detailed methods of the exact number of participants included, specifications of experimental design, methodology and statistical analysis used. Taken together, this thesis draws on an integration of methodological approaches used to advance the scientific study of anosognosia (see Fotopoulou, 2012). Accordingly, a combination of methods will be draw on in the chapters to follow, specifically: neuropsychological testing, psychophysiological experiments and neuroimaging methods.

Chapter 3 The affective modulation of motor awareness in anosognosia

3.1 Introduction

One facet of anosognosia for hemiplegia (AHP) that has received less empirical attention, despite a long history of clinical observations and theoretical debates (Weinstein & Kahn, 1955; Bisiach & Geminani, 1991), is the role of emotional factors. On clinical examination, patients typically manifest some degree of blunted affect or ‘indifference’ for their paralysis and its consequences. This indifference (anosodiaphoria; Babinski, 1914) can exist with or without concomitant explicit denial of deficits. On the contrary, depressive symptoms and ‘catastrophic reactions’ (sudden influx of strong, negative feelings and related behaviours; Goldstein, 1939) are encountered rarely. Moreover, there are some clinical indications that as unawareness decreases over time, depressive symptoms begin to emerge in patients who were previously emotionally unresponsive towards their paralysis (Fotopoulou et al., 2009; Kaplan-Solms & Solms, 2000). Exceptionally, some patients with or without explicit denial of deficits have been noted to show a strong hatred towards their paralysed limbs (misoplegia; Critchley, 1974), or a disproportionate exasperation with irrelevant, minor disappointments, despite their apparent indifference for their paralysis (Weinstein & Kahn, 1950; Kaplan-Solms & Solms, 2000; Fotopoulou & Conway, 2004).

Some authors have argued that this lack of affect, or misattribution of negative emotions, is caused by purely psychogenic ‘defence’ mechanisms. According to the now classic theory of Weinstein and colleagues (e.g. Weinstein & Kahn, 1955; Weinstein, 1991), denial and related premorbid coping mechanisms prevent patients from explicitly acknowledging their paralysis, and self-attributing the associated negative emotions. Alternatively, this lack of emotional reactivity has been considered to be the direct consequence of damage to the right (frontal) hemisphere, regarded by some authors as specialised for the processing of negative, withdrawal-related emotions (Davidson, 2001; see Gainotti, 2012 for review). However, neither of these two approaches has been fully supported by empirical evidence. Specifically, the psychodynamic account of AHP fails to explain the relative neuroanatomical and behavioural specificity of anosognosic behaviours (Bisiach & Geminani, 1991; Heilman & Harciarek, 2010). The ‘valence’ hypothesis has similarly not been supported in the literature; although patients with AHP do typically score lower than control patients in self-report measures of depression and anxiety (e.g. Fotopoulou et al., 2010), more sensitive investigations have shown that they

do not differ from controls groups in their ability to experience such emotions (Turnbull et al., 2005; Vocat et al., 2010). They also show appropriate, negative emotional reactions to their deficits when the latter are evoked implicitly (Nardone et al., 2007; Fotopoulou et al., 2010). Thus, it appears that the relation between AHP and emotion is more complex than suggested by either the psychodynamic or the valence hypothesis.

More generally, such rigid distinctions between purely psychodynamic and neurocognitive explanations have been challenged recently (Fotopoulou, 2012) and integrative accounts of AHP have been put forward (Fotopoulou, 2014; Turnbull et al., 2005; Turnbull et al., 2014; Vuilleumier, 2004). According to such theories, complex imbalances between cognition and motivation may be caused directly by damage to insular, striatal, or limbic regions that have recently been found to be selectively associated with AHP (Fotopoulou et al., 2010; Vocat et al., 2010; Moro et al., 2011). For example, Vuilleumier and colleagues have suggested that damage to the basal ganglia may obstruct the “discovery” of deficits, as patients have reduced affective drive to respond to errors and revise beliefs based on new perceptual evidence (Vuilleumier, 2000, 2004; Vocat et al., 2013). Similarly, within a computational framework, Fotopoulou and colleagues have suggested that insular and basal ganglia damage may lead to weak and imprecise signals about the physiological condition of one’s body. This leads to aberrant ‘top-down’ inferences about bodily states, and difficulties in affectively personalising new sensorimotor information (Fotopoulou, 2014).

Taken together, these accounts suggest that the lack or misattribution of negative emotions in AHP relates to impairments in higher-order cognition, rather than to primary deficits in emotional processing. This ‘top-down’ perspective is consistent with a relatively neglected facet of AHP, namely, the fluctuations of awareness based on the emotional or social context in which awareness is probed. For instance, Kaplan-Solms and Solms (2000, see also Turnbull, Jones & Reed-Screen, 2002; Ross & Rush, 1981; Starkstein & Robinson, 1988) have shown that when themes of loss are explored during psychotherapeutic sessions – particularly when such loss is apparently unrelated to their disabilities – transient awareness and depressive episodes can be experienced by patients that are otherwise stably anosognosic. Marcel and colleagues (2004) have further shown that awareness may increase in some patients when they are asked about their disabilities in an emotional, conspiratory manner, or from the perspective of the examiner (also see Fotopoulou et al., 2009, 2011; Fotopoulou, 2014). Notwithstanding the theoretical interest

of these observations, to the investigators knowledge there is no systematic, experimental investigation of the moderating role of emotional and social context in AHP.

Accordingly, this study aimed to investigate the relation between emotion and motor awareness in AHP. To this end, right-hemisphere stroke patients with AHP and control patients without AHP were recruited. Motor awareness was assessed before and after, providing positive and negative feedback about performance on a standardised cognitive test (the Hayling Test; Burgess & Shallice, 1997). The task includes components of varied difficulty that made it possible to match with the valence of the provided feedback to generate realistic conditions of positive and negative feedback. Moreover, it is unrelated to motor abilities so the role of emotion on motor awareness could be tested, without being uncomplicated by ‘bottom-up’ sensorimotor signals and the patients’ explicit or implicit feelings about their motor abilities. Based on the idea that patients with AHP have lost the ability to use signals from their own body to make related inferences about their current bodily state (Fotopoulou, 2014; see also above), the main aim was to test whether the ‘top-down’ experimental induction (by verbal, social feedback) of negative feelings about oneself could improve awareness of one’s motor disabilities. It was expected that patients with AHP would show increased awareness of their deficits following negative feedback compared with positive feedback, while such effects were not expected in the control group. Furthermore, in order to ensure that the experimental feedback had induced the desired emotions in patients, patients’ self-reported emotional state was measured following each condition of the main task. If patients with AHP were capable of experiencing negative emotions, it was expected that negative feedback would lead to more negative feelings than positive feedback in both patient groups.

Lastly, this study examined whether lesions to critical cortical (premotor and the insular cortex) and subcortical (basal ganglia and limbic structures) areas would be associated with increased unawareness scores, as in previous studies (Berti et al., 2005; Karnath et al., 2005; Fotopoulou, et al., 2010; Moro et al., 2011). Contrary to such lesion subtraction investigations, however, a voxel-based lesion-symptom mapping (VLSM) approach was used (Bates et al., 2003; Rorden et al., 2007). This method was used to identify the brain regions associated with a change in motor awareness induced by the experimental task, which according to the presented hypothesis should include the insula ribbon and basal ganglia structures (Fotopoulou, 2014; Vuilleumier, 2004; see also above). While the first

clinico-anatomical correlation has been investigated before in the literature, to the investigators knowledge, only two previous studies have investigated the association between behaviour on carefully-controlled experimental conditions and neuroanatomical data (Fotopoulou et al., 2010; Moro et al., 2011), and no study has examined this association in relation to emotion.

3.2 Methods

3.2.1 Patients and assessment of anosognosia

A total of 16 patients took part in the study (nine women; mean age = 68.19, SD = 14.27 years, age range: 41-88). Patients were recruited from consecutive admissions to two acute stroke wards according to the inclusion criteria specified in Chapter 2. Two additional sets of patients were recruited subsequently in order to test (see Section 3.2.3): (i) a control condition in which the order of experimental conditions was reversed ($n = 2$; two women with AHP, 82 and 90 years of age); and (ii) the specificity of the effect to motor awareness ($n = 3$; two patients without AHP, 57-year-old male and 70-year-old female, and one female AHP patient, 84 years of age).

Eight of the 16 patients were classified as having AHP (four women; mean age = 71.63, SD = 16.18 years, age range: 41-88) and eight were classified as right-hemisphere controls (HP group; five women; mean age = 64.75, SD = 12.14 years, age range: 47-78). This classification was based on the Berti et al. (1996) interview, as described in Chapter 2. The Feinberg et al. (2000) scale, also explained in Chapter 2, was used as a secondary measure of unawareness to confirm the diagnosis and rate the severity of unawareness.

3.2.2 Neurological and neuropsychological assessment

In addition to the anosognosia assessment above, all patients were tested using standard neurological and neuropsychological assessments, which have been described in detail in Chapter 2. Tests included: assessments of motor strength for both upper and lower limb; proprioception; visual and tactile extinction; premorbid intelligence, general cognitive function, orientation and mood tests; working memory, long-term verbal recall, and executive functioning tests; and personal as well as visual-spatial neglect tests.

3.2.3 Experimental study design

The main experimental aim was to induce positive and negative emotions in patients with AHP and HP controls, and assess their effects on motor awareness. To this end, a standardised cognitive task was administered, the Hayling Sentence Completion Test of executive functioning (Burgess & Shallice, 1997), which entails two similar tasks varying in difficulty. Namely, a simple, sentence completion task (measuring processing speed), and a more difficult sentence completion task, in which patients have to provide responses that are unrelated to the meaning of the sentences (measuring inhibition of automatic responses). Healthy controls and particularly neurological populations are known to perform faster on the first task, and with fewer errors, compared with the second task (Burgess & Shallice, 1997; see Results section below for confirmation of this result in the sample). In order to ensure the induction of positive and negative feelings respectively, explicit, verbal feedback provided by the experimenter was further manipulated after each trial: positive feedback was provided following trials of the easy task, and negative feedback was provided following trials of the difficult task. Hence, feedback could be administered ‘realistically’ and ensure construct validity. This feedback manipulation can be understood as a mood induction procedure (Nummenmaa & Niemi, 2004), widely used in psychological research, including with neurological patients (e.g. Mograbi, Brown, Salas, & Morris, 2012). As in Mograbi et al. (2012), the induced emotions are considered short lived and fall within the normal range of emotional experience (Frost & Green, 1982; Isen & Gorgoglione, 1983; Martin, 1990). This was confirmed in this sample at debriefing (see Procedures Section 3.2.5 below).

The experiment had a 2 (Group: AHP vs. HP) x 2 (Emotion: positive vs. negative feedback) mixed factorial design, with Emotion as the within-subjects factor. Due to the nature and the standardised administration order of the Hayling Test (Part 1: the easier sentence completion task is followed by Part 2: the harder sentence completion task) positive feedback preceded negative feedback in the experiment. Thus, to examine possible order effects, a control experiment in two additionally recruited AHP patients was conducted, in whom the order of positive and negative feedback was reversed (i.e. first administering Section 2 with negative feedback, and then Section 1 with positive feedback).

Finally, in order to determine the specificity of the emotion induction on motor awareness an additional control experiment was conducted with three right-hemisphere damaged

patients. The experimental procedure was identical to the above, with the exception of additional pre-and-post measures to assess any changes in visuospatial neglect, personal neglect, and anosognosia for drawing neglect, in addition to motor awareness. Specifically, changes in neglect were assessed by administering the copy, line bisection and star cancellation subtests of the BIT (Wilson et al., 1987) and the ‘one-item test’ (Bisiach et al., 1986) pre-and-post the positive and negative emotion induction. Four additional questions were added to the motor awareness questionnaire (please see below) to assess awareness of drawing neglect (Berti et al., 1996). Referring to their performance on the ‘copy’ subtest of the BIT (administered before the experiment; Wilson et al., 1987) patients were asked: (i) two general questions (e.g. “Are you happy with your drawing of the Daisy?” and “Are the daisies alike?”); and (ii) to provide subjective ratings of their drawing performance using a 11-point Likert-type scale (e.g. “Using this scale from 0-10, how good is the drawing, 0 being not good at all and 10 being very good?” and “Using this scale from 0-10, how alike are the drawings, 0 being not at all alike and 10 being exactly the same?”).

3.2.4 Measures

The primary dependent variable was ‘awareness change’, which was based on a motor awareness questionnaire, developed based on pre-existing, validated measures (e.g. Berti et al., 1996; Marcel et al., 2004), and administered immediately before and after each Emotion condition. Previous studies have suggested that AHP patients may ‘learn’ the ‘correct’ responses to answers on awareness measures when repeatedly administered (Marcel et al., 2004). To avoid such repetition confounds, four equivalent versions of the questionnaire were developed. Each version comprised of seven items, covering four domains: (i) two general awareness questions (e.g. “Do you have any weakness anywhere?”); (ii) one question related to left unimanual ability, followed by a ‘confrontation’ and ‘check’ question (e.g. “Can you wave to me with your left hand? Please do it for me now. Have you done it?”); (iii) one question concerning bimanual action ability, each followed by confrontation and check questions (e.g. “Can you tie a knot? Please do it for me now. Have you done it?”), and (iv) one bipedal awareness question (e.g. “Can you climb a ladder?”). Each question was scored according to the method of Feinberg et al. (2000): 0 = no unawareness; 0.5 = partial unawareness; and 1.0 = complete unawareness; therefore, higher scores indicated greater unawareness (range = 0-7). For each Emotion condition (i.e. positive and negative feedback), the post-induction

awareness score was subtracted from the pre-induction awareness score of each patient, to obtain a main measure of *awareness change*.

Additionally, in order to evaluate the effects of emotional feedback on patients' emotional state *per se*, patients were asked to provide a subjective rating of their current emotional state on a 6-point Likert-type scale (i.e. "Using this scale from zero to five, zero being very unhappy and five being very happy, how do you feel right now?"). The scale was read aloud to patients and also presented visually as a vertical scale on an A4 sheet of paper (0 at the bottom and 5 at the top), positioned in the patient's right visual field in order to minimise possible unilateral visual neglect effects. Patients were familiarised with the rating scale before the experiment.

3.2.5 Procedures

The experiment was organised into two phases: [i] administration of Hayling Test Part 1 (simple sentence completion) with positive feedback, and [ii] administration of Hayling Test Part 2 (inhibition of automatic response) with negative feedback. These were conducted in a single session, separated by a 30-minute interval, during which standard neuropsychological tests (see above) were administered without feedback. Part 1 of the Hayling Test requires the patient to complete a series of sentences with the last word missing from it as fast as possible (e.g. "The rich child attended a private...", response: school). The response and reaction time are recorded and the total time score is converted into a scaled score. In part 2, the patient is again asked to complete a series of sentences as above, but their response is to be completely unconnected to the sentence (e.g. "London is a very busy...", possible response: banana). The response and the reaction time are recorded, and the total time and response errors are converted into a scaled score.

Positive feedback was provided in a standardised manner, using one of the following seven statements, in a pseudorandomised order: (i) "Well done", (ii) "That is correct", (iii) "Your answer was very quick", (iv) "Excellent work", (v) "You are doing so well on this task", (vi) "Very impressive", and (vii) "Your performance has been excellent so far". Positive feedback was matched to performance as much as possible, i.e. most answers were correct and given within one minute and hence one of the above statements was provided. In the unlikely event that an answer was wrong, statement (iii) was provided; or, if an answer was very slow (more than one minute), this statement was not used and one of the other statements were provided. It is also important to highlight that,

although this feedback was realistic in all cases, it was pre-selected and false in the sense that it did not correspond to the norms of the Hayling Test.

Similarly, negative feedback was provided using one of the following seven standard statements: . (i) “That is incorrect”, (ii) “You are not doing very well on this task”, (iii) “Your performance has been very poor so far”, (iv) “That is the wrong answer”, (v) “You are doing poorly so far”, (vi) “Your answer was too slow”, and (vi) “You are not performing very well”. Feedback was consistent with patients’ actual performance as much as possible (in the same manner as above, but matched to the poor performance of patients).

Measures of awareness were taken immediately before (i.e. pre-induction awareness) and after (i.e. post-induction awareness) the two parts of the task. The emotion rating scale was completed after each post-induction awareness questionnaire, in order not to influence the latter. During the control experiment, the procedures were identical to the above, except for reversing the order of phases one and two.

Patients were carefully and fully debriefed following completion of the experiment; the purpose of the positive and negative feedback were fully explained, and any questions were addressed. It was stressed that the feedback provided did not reflect their actual performance on the Hayling Task, as determined by the available, standardised norms, or by the face value impressions the task itself might generate. Any ongoing emotional distress (if experienced) was fully discussed and reflected upon to ensure that the patients’ emotional state was stable. There were no particularly strong reactions during the experiment, or following debriefing, and none of the patients reported having guessed or suspected the manipulation.

3.2.6 Statistical analysis

All behavioural analyses were conducted in Stata 11 (StataCorp, 2011). Independent samples *t*-tests were used to analyse mean differences between groups on neuropsychological tests. Items that were not normally distributed were also analysed using the non-parametric equivalent (Mann-Whitney *U* test) to confirm the findings (see Appendix G).

Analysis of main experiment

The differential ‘awareness change’ scores (see Measures, Section 3.2.4) were used as the outcome measure in all analyses, which were conducted using multiple linear regression. The awareness change data were not normally distributed, hence bootstrapping with 1000 repetitions was applied (bootstrapping makes no assumption as to the distribution of the data; Guan, 2003); bootstrapped standard errors (SE) are therefore reported. The same analysis was also run while co-varying for overall negative mood (HADS depression scores, as these were found to differ between the groups, see below). Preliminary examination of the awareness change data identified one HP control patient scoring more than two SD above the group mean, and hence this patient was removed from subsequent experimental analyses as an outlier.

Analysis of control variables

A multiple linear regression (as above) on emotion ratings was used to investigate whether patients experienced a change in their emotional state in the two feedback conditions. The same analysis was also run while co-varying for overall negative mood (HADS depression scores). Furthermore, to ensure there was no difference in the baseline awareness scores preceding the positive and negative feedback conditions (particularly given the fixed order of the task), non-parametric tests were conducted that compared the baseline awareness scores preceding the positive and the negative feedback conditions in each group. In addition, a comparison between groups of the total scaled scores of the Hayling Sentence Completion test was conducted, as well as the scaled scores for Part 1 and 2, to ensure the actual performance of both groups was consistent with the task’s expected difficulty levels, and that the provided feedback was realistic and of similar relevance to both groups. Additionally, modified t-tests (SINGLIMS_ES; Crawford, 2010; Crawford et al., 2002; Crawford et al., 1998) were used to determine whether the awareness change scores of the two AHP patients in the reverse-order experiment (see Section 3.2.3) differed significantly from those of the HP group. Finally, in order to investigate whether any changes in awareness resulting from the experiment had a lasting effect, non-parametric tests were used to compare Feinberg awareness scores acquired on initial assessment (prior to the experimental session) with those obtained one-to-three days after the experiment was conducted.

3.2.7 Lesion analysis methods

Routinely acquired clinical CT ($n = 10$) and MRI ($n = 5$) data sets were obtained within the first week of admission. The clinical data set of one HP control patient was unavailable and the patient was therefore excluded from further imaging analyses. Lesion mapping methods detailed in Chapter 2 were used for the analysis below. The VLSM analysis (Bates et al., 2003; Rorden et al., 2007) was used to identify anatomical regions associated with: i) the presence of anosognosia (Feinberg awareness scores, inverted to adhere with the NPM prerequisite of the directionality of the input data) and ii) the awareness change induced by the experimental design ('change in awareness' scores for the negative emotion induction). For these behavioural measures a lower score indicates lower awareness and less awareness change following negative emotion induction, respectively.

3.3 Results

3.3.1 Demographic and neuropsychological results

Patients' demographic characteristics and their performance on standardised neuropsychological tests are summarised in Table 3.1. The groups did not differ significantly in terms of age, education or symptom onset to assessment interval. As expected, there was a significant difference in awareness scores between the AHP and HP groups on both the Berti et al. (1996) interview ($t(14) = 5.60, p < 0.001$) and the Feinberg et al. (2000) scale ($t(14) = 7.06, p < 0.001$). The groups showed similar sensory deficits, as well as similar impairments in general cognitive functioning, abstract thinking, reasoning abilities and neglect. Although both groups showed deficits in proprioception, the AHP group was significantly more impaired ($t(12) = 2.33, p = 0.04$). The AHP group showed significantly lower scores for depression on the HADS when compared to controls ($t(14) = 3.06, p = 0.01$). This difference was taken into account in subsequent analyses

Table 3.1 *Groups' demographic characteristics and neuropsychological profile*

| | AHP(n=8) | | HP(n=8) | | t-Test | | |
|-------------------------------------|--------------------|-------|--------------------|-------|--------|-------|-------|
| | Mean | SD | Mean | SD | t | df | p |
| Age (years) | 71.63 | 16.18 | 64.75 | 12.14 | 0.96 | 14.00 | 0.35 |
| Education (years) | 11.88 | 1.81 | 12.63 | 1.92 | 0.68 | 14.00 | 0.51 |
| Days from onset | 11.13 | 11.26 | 14.38 | 10.56 | 0.60 | 14.00 | 0.56 |
| MRC Left upper limb | 0.25 | 0.46 | 0.38 | 0.52 | 0.51 | 14.00 | 0.62 |
| MRC left lower limb | 0.63 | 0.92 | 1.00 | 1.07 | 0.75 | 14.00 | 0.46 |
| Premorbid IQ-WTAR | 41.50 | 7.79 | 33.00 | 7.62 | 1.41 | 10.00 | 0.19 |
| Berti awareness interview | 1.63 | 0.52 | 0.25 | 0.46 | 5.60 | 14.00 | 0.00* |
| Feinberg awareness scale | 6.31 | 2.17 | 0.63 | 0.69 | 7.06 | 14.00 | 0.00* |
| Orientation | 2.88 | 0.35 | 3.00 | 0.00 | 1.00 | 7.00 | 0.35 |
| Digit span forwards | 5.63 | 1.19 | 6.13 | 0.99 | 0.91 | 14.00 | 0.38 |
| Digit span backwards | 2.88 | 0.83 | 3.38 | 1.30 | 0.91 | 14.00 | 0.38 |
| MOCA memory | 3.75 | 0.89 | 4.17 | 0.98 | 0.83 | 12.00 | 0.42 |
| MMSE | 22.20 | 6.02 | 25.00 | 2.16 | 0.88 | 7.00 | 0.41 |
| Visual fields | 4.29 ^a | 1.89 | 3.57 ^a | 1.99 | 0.69 | 12.00 | 0.50 |
| Somatosensory (max 6) | 3.38 ^a | 1.41 | 3.00 ^a | 1.60 | 0.50 | 14.00 | 0.63 |
| Proprioception (max 9) | 3.71 | 2.21 | 6.57 | 2.37 | 2.33 | 12.00 | 0.04* |
| Comb/razor test left | 4.75 | 4.13 | 5.25 | 2.60 | 0.29 | 14.00 | 0.78 |
| Comb/razor test right | 12.63 | 5.10 | 10.63 | 2.97 | 0.96 | 14.00 | 0.35 |
| Comb/razor test ambiguous | 5.88 | 1.96 | 4.13 | 2.42 | 1.59 | 14.00 | 0.13 |
| Bisiach one item test | 0.75 | 0.46 | 0.38 | 0.52 | 1.53 | 14.00 | 0.15 |
| Line crossing right | 11.50 | 6.44 | 16.25 | 2.05 | 1.99 | 8.41 | 0.08 |
| Line crossing left | 6.75 ^a | 8.14 | 10.00 ^a | 8.68 | 0.77 | 14.00 | 0.45 |
| Star cancellation right (omissions) | 13.75 | 6.11 | 11.00 | 6.19 | 0.89 | 14.00 | 0.39 |
| Star cancellation left (omissions) | 21.25 ^a | 10.43 | 18.88 ^a | 10.86 | 0.45 | 14.00 | 0.66 |
| Copy | 0.50 ^a | 0.76 | 1.00 ^a | 1.07 | 1.08 | 14.00 | 0.30 |
| Representational drawing | 0.25 | 0.46 | 0.50 | 0.53 | 1.00 | 14.00 | 0.33 |
| Line bisection right | 0.43 ^a | 0.53 | 0.38 ^a | 0.52 | 0.20 | 13.00 | 0.85 |
| Line bisection centre | 0.57 ^a | 0.53 | 0.75 ^a | 0.46 | 0.69 | 13.00 | 0.50 |
| Line bisection left | 0.38 ^a | 0.52 | 0.50 ^a | 0.53 | 0.48 | 14.00 | 0.64 |
| Cognitive estimates | 16.71 ^a | 4.86 | 15.50 ^a | 2.26 | 0.56 | 11.00 | 0.59 |
| FAB total score | 11.40 ^a | 2.70 | 13.50 ^a | 2.51 | 1.43 | 11.00 | 0.18 |
| HADS depression | 2.88 | 2.70 | 8.00 ^a | 3.89 | 3.06 | 14.00 | 0.01* |
| HADS anxiety | 5.13 | 3.00 | 7.25 | 4.89 | 1.05 | 14.00 | 0.31 |

Medical Research Council (Guarantors of Brain, 1986); MOCA=The Montreal Cognitive Assessment (Nasreddine, 2005); Comb/razor test = tests of personal neglect (McIntoch et al., 2000); Bisiach one item test= test of personal neglect; Visual fields and somatosensory= customary 'confrontation' technique= Bisiach et al. (1986); line crossing, star cancellation, copy & representational drawing= conventional subtests of Behavioural Inattention Test (Wilson et al., 1987); FAB= Frontal Assessment Battery (Dubois et al., 2000); HADS=Hospital Anxiety and Depression scale (Zigmond, & Snaith,1983)

^a Scores below tests' cut-off points, or more than 1 SD below average mean.

*Significant difference between groups, $p<0.05$

3.3.2 Main experimental results: awareness change

A linear regression analysis revealed a significant main effect for the factor Group ($b = 2.04$, $SE = -0.45$, $p < 0.001$, 95% CI = 1.16; 2.92), with the AHP group showing a greater change in awareness (marginal mean = 0.99) compared with the HP group (marginal mean = -0.02). Also, a significant main effect of Emotion induction type ($b = -1.07$, $SE = 0.46$, $p = 0.019$, CI = -1.96; -0.18) was observed, with awareness change being significantly greater following the negative (marginal mean = 1.6) compared with the positive emotional induction (marginal mean = -0.57). The interaction between Emotion induction type and Group was also significant ($b = -2.05$, $SE = 0.61$, $p = 0.001$, CI: -3.26; -0.84), with the AHP group (marginal mean = 2.55) showing a greater change in awareness compared with the HP group (marginal mean = 0.75) following the negative emotional induction only (see Figure 3.1). Taking the HADS depression scores into account in this analysis did not change the pattern of these results.

A qualitative example of the change in motor awareness observed as a result of the emotion induction is described here. During the pre-awareness assessment one patient stated “*No, I have no weakness anywhere, no*”, claiming that “*I can move my arm, no problem*” and was adamant that she raised her left arm and clapped her hands. Following the negative emotion induction, the same patient admitted that her left arm “*is not as strong as before the stroke*”, saying “*I don’t think I can move this arm now, it feels weak*”. When asked if she can tie a knot, she replied “*I’m not so sure now*” and after attempting the action, she observed “*no, I can’t do that.*”

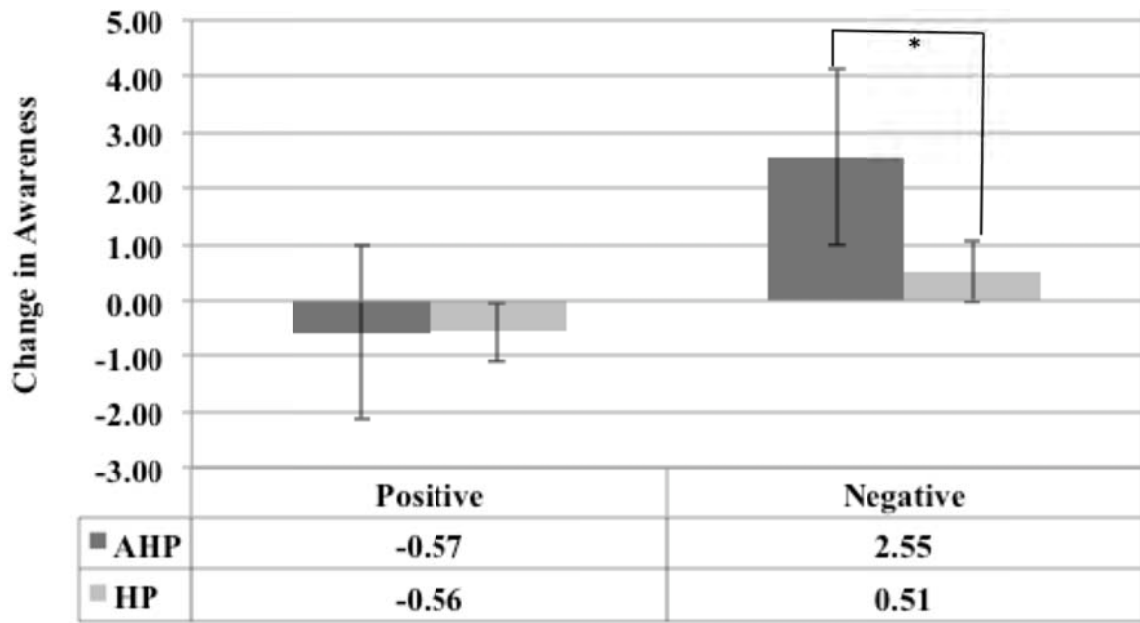


Figure 3.1 *Change in awareness scores after emotional induction*

Note: Marginal means and interquartile range (error bars) of the change in awareness for the AHP (dark grey bars) and HP (light grey bars) groups after the positive and negative emotional induction: * $p < 0.05$. The Y-axis indicates the change in awareness scores analysed by calculating the difference in awareness scores between each condition (post minus pre) for each group. Positive scores indicate an increase in awareness (i.e. less anosognosia) and negative scores indicate a decrease in awareness (i.e. more anosognosia).

3.3.3 Emotional state induction

To investigate whether patients experienced a change in their emotional state following the positive and negative induction respectively, we examined the main effects of Emotion (positive vs. negative feedback) and Group (AHP vs. HP) on emotion ratings. The regression analysis confirmed a main effect of Emotion ($b = 1.83$, $SE = 0.439$, $p < 0.001$, $CI: 0.97; 2.69$) with patients giving significantly lower emotion ratings (i.e. reporting feeling less happy) following the negative emotional induction (marginal mean = 2.17) compared with the positive emotional induction (marginal mean = 3.83). The model also showed that the factor Group significantly predicted emotion ratings ($b = 0.99$, $SE = 0.49$, $p = 0.046$, $CI: 0.019; 1.97$), with AHP patients showing more positive emotion ratings (marginal mean = 3.41) compared with right-hemisphere controls (marginal means = 2.59). However, there was no significant interaction between the factors induction type and group ($b = -0.33$, $SE = 0.64$, $p = 0.6$, $CI: -1.59; 0.93$; see Figure 3.2).

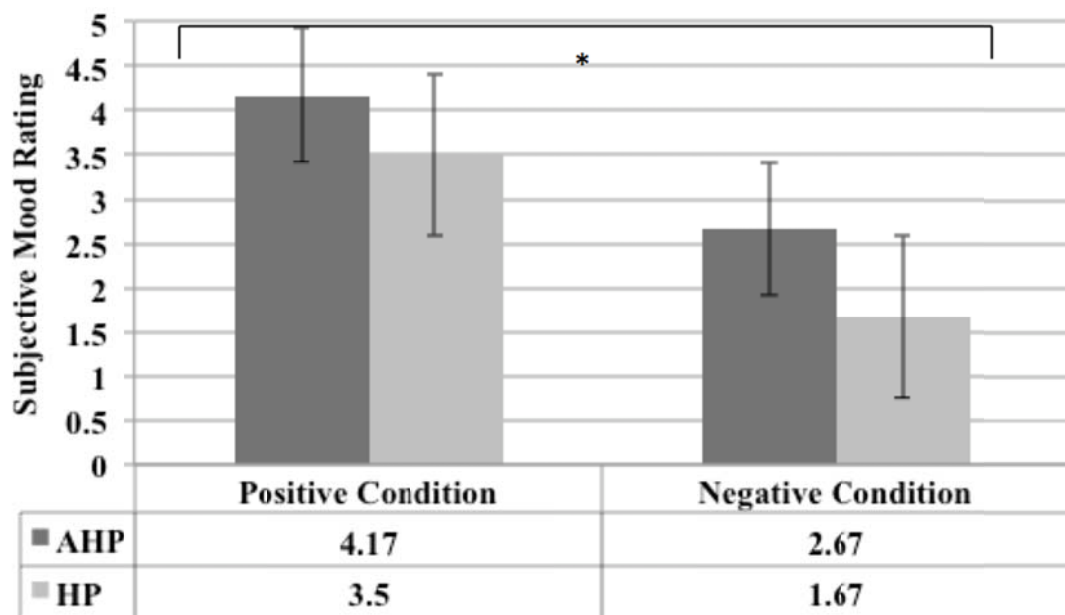


Figure 3.2 *Emotion ratings after emotional induction*

Note: Marginal means and interquartile range (error bars) of emotion ratings for AHP (Dark grey bars) and HP (light grey bars) groups after positive and negative mood induction: * $p < 0.05$. The Y-axis indicates the patient's subjective mood ratings on a scale from zero to five (0 = very unhappy; 5 = very happy).

3.3.4 Baseline awareness scores

A Wilcoxon Signed Rank Test revealed that there was no significant difference between pre-awareness scores of the positive (median = 2) and of the negative condition overall (median = 3, $Z = -0.27$, $p = 0.82$, $r = 0.067$). This applied also to the AHP group ($Z = -0.9$, $p = 0.563$, $r = 0.23$) and the HP group ($Z = -0.7$, $p = 0.75$, $r = 0.18$), in respective, separate analyses.

3.3.5 Performance on Hayling test

Analysis of the Hayling Sentence Completion Test using a Mann-Whitney U test showed no significant difference between total scaled scores of the AHP and HP groups ($Z = -1.14$, $p = 0.28$, $r = 0.29$). According to the tests norms, overall scaled scores indicated that the AHP group's performance was 'low average' (median = 4), while the HP group's performance was 'moderate average' (median = 5). Similarly, there was no difference found in Hayling part 1 ($Z = -0.9$, $p = 0.42$, $r = 0.23$), with the scaled score for completion time being 'low average' for the AHP group (median = 4) and 'moderate average' for the HP group (median = 5). This again applied to Hayling part 2, with no difference found between groups in their total scaled score for completion time ($Z = -0.4$,

$p = 0.8$, $r = 0.1$) and response errors ($Z = -1.1$, $p = 0.31$, $r = 0.28$), with the AHP group performing ‘average’ for time (median = 6) and ‘abnormal’ for response errors (median = 1.5). Similarly, the HP group performed ‘average’ for time (median = 6) and ‘abnormal’ for responses errors (median = 2). Therefore, the feedback given was realistic based on patients’ actual performance, with both groups performing better on part 1 than on part 2, and showing no differences between groups on either part.

3.3.6 Reverse order control condition

The two AHP patients who performed the experiment in the reverse order showed the same pattern of results as found in the main group analysis. After the negative emotion induction, both patients showed a greater improvement in awareness (AHP09: mean = 5, AHP10: mean = 3.5) compared to the control group (mean = 0.5; SD = 0.82; AHP09: $t(7) = 5.13$, $p = 0.001$, $r = 5.49$; AHP10: $t(7) = 3.42$, $p = 0.007$, $r = 3.66$). There was no difference between either AHP patient and the HP control group in awareness change following positive emotion induction (AHP09: $t(7) = 0.45$, $p = 0.33$, $r = 0.48$; and AHP10: $t(7) = 1.7$, $p = 0.07$, $r = 1.81$).

3.3.7 Specificity of effect control condition

The three patients with right-hemisphere damage who performed this additional control experiment showed no change in personal neglect assessments, and a minor change in visuospatial neglect, with extrapersonal neglect becoming slightly worse following negative versus positive induction in two patients. Additionally, there was a non-mood specific improvement in awareness of neglect in one patient. The results are summarised in 3 case reports below (see Appendix H for a summary of results). Patient HP09 presented with no AHP, no personal neglect, no visuospatial neglect except on the ‘copy’ subtest, and mild unawareness of drawing neglect. There was no change in visuospatial and personal neglect, or awareness of drawing neglect following the positive and negative emotion induction condition. Patient HP10 presented with no AHP, mild personal neglect, visuospatial neglect and unawareness of drawing neglect. She showed no change in the line bisection subtest, personal neglect scores, and general questions for awareness of drawing neglect, but a small increase in visuospatial neglect following the positive and negative emotion induction conditions. There was also a small increase in awareness of drawing neglect following the negative emotion induction, but a much larger increase in awareness following positive induction. Lastly, patient AHP11 presented with AHP, personal neglect, visuospatial neglect and mild unawareness of drawing neglect. There

was no change in her personal neglect and awareness of drawing neglect scores, and no change in her performance on the line bisection subtest following the negative and positive emotion inductions. There was a small increase in visuospatial neglect (star cancellation subtest) following the negative but not positive emotion induction.

3.3.8 Follow-up awareness testing

Wilcoxon signed rank test showed that there was no significant difference in Feinberg awareness scores before and after the experiment, in either the AHP ($Z = -0.45$, $p = 0.66$, $r = 0.12$) or HP group ($Z = -1.63$, $p = 0.1$, $r = 0.42$), suggesting that the observed awareness changes were temporary and experimental effects, rather than permanent, clinical changes.

3.3.9 Lesion analysis

All lesions resulted from a first-ever unilateral stroke, mainly within the right middle cerebral artery territory. Group-level percentage lesion overlay for the AHP group ($n = 8$) identified the involvement of cortical and subcortical areas, comprising the inferior and superior frontal gyri, the pericentral cortex, the insula ribbon, and the internal capsule (see Figure 3.3A). In comparison, the lesion overlap map for the HP group ($n = 7$) revealed a more focal lesion pattern involving mainly subcortical regions (see Figure 3.3B). Lesion volume (in cubic centimetres) was not significantly different between the AHP group (mean = 4.64, SD = 5.47) and the HP group (mean = 3.25, SD = 4.19; $t(15) = 0.55$, $p = 0.594$). The lesion subtraction map identified mainly the anterior and posterior insular ribbon, the posterior basal ganglia, and dorsal pericentral areas to differ between the groups (see Figure 3.3C).

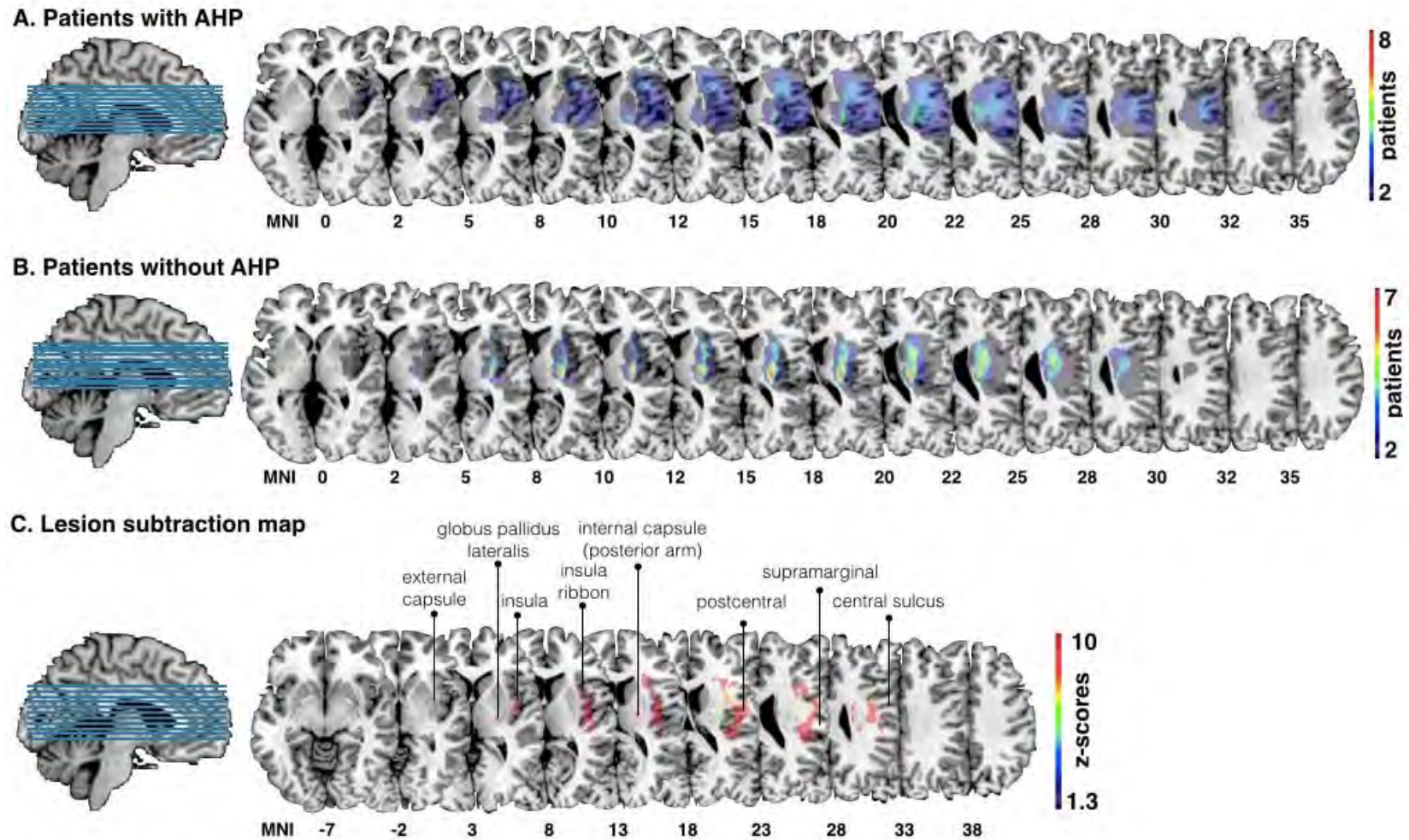
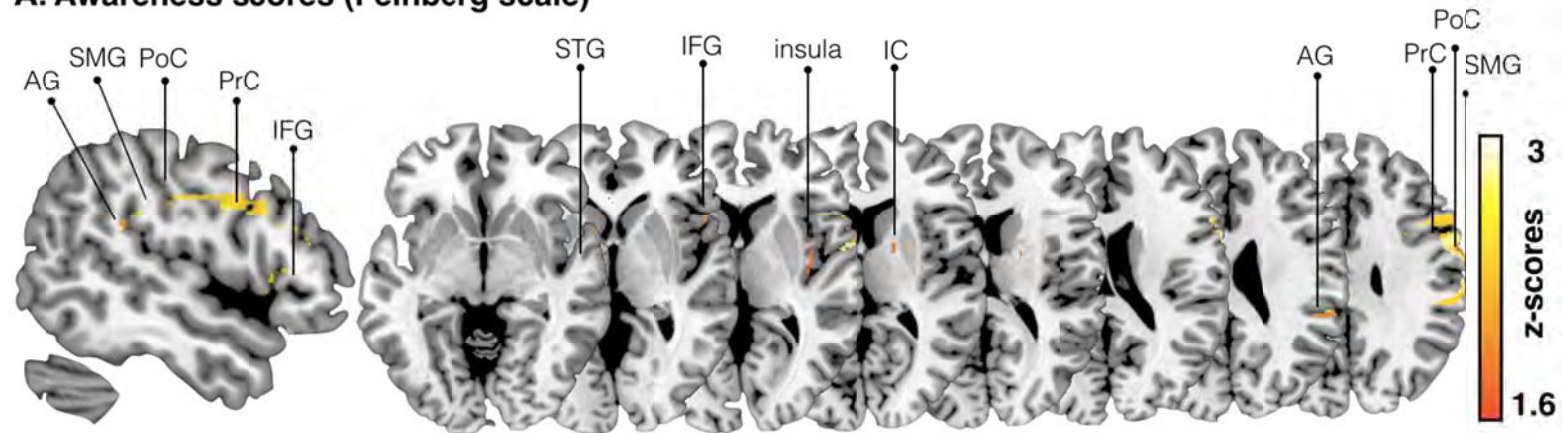


Figure 3.3 Group-level lesion overlay maps for patients with anosognosia for hemiplegia (AHP) and hemiplegic (HP) controls

Note: **A.** Overlay of lesions in patients with anosognosia (AHP; $n=8$); **B.** Overlay of patients without anosognosia ($n=7$). **C.** Statistical analysis comparing the two populations of patients (AHP present-AHP absent; results are corrected for multiple comparisons, $p < 0.05$ for $Z > 1.3$)

VLSM analysis using the continuous Feinberg awareness scores, revealed that voxels within the posterior insula, the supramarginal, the angular and superior temporal gyrus (SMG, AG and STG), internal capsule, pericentral gyri, and the inferior frontal gyrus (IFG) were significantly associated with differences in awareness ($p < 0.05$) (see Figure 3.4A). Similar results were found when co-varying lesion size. Additionally, VLSM analysis, looking at the experimental change in awareness scores (i.e. differential scores following negative emotional induction only), without and with co-variation of lesion size, identified significant voxels ($p < 0.05$) within the anterior arm of the internal capsule, the anterior insula, the anterior lateral putamen with a lateral extension into the external capsule and an additional region in the dorsal anterior periventricular white matter (likely to contain limbic white matter connections; see Figure 3.4B).

A. Awareness scores (Feinberg scale)



B. Change in Awareness (Differential Scores)

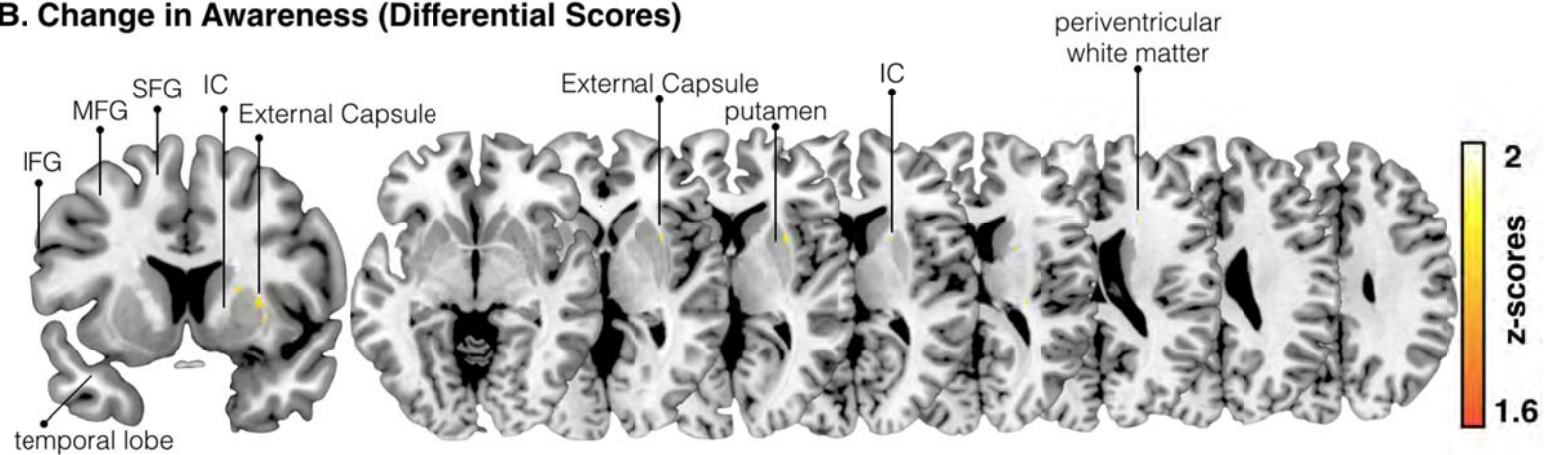


Figure 3.4 Voxel-based lesion symptom (VLSM) analysis for Feinberg scale and change in awareness following negative emotion induction

Note: **A.** Damaged MNI voxels predicting the severity of unawareness of symptom deficits (Feinberg scale, inverted, continuous measure; $p < 0.05$ for $Z > 1.64$). **B.** Damaged MNI voxels predicting the change in awareness (differential scores: pre - post mood induction; continuous measure; $p < 0.05$ for $Z > 1.64$).

PrC=precentral, PoC=postcentral, SMG=supramarginal, STG=superior temporal gyrus, IFG=inferior frontal gyrus, IC=internal capsule, MFG, middle frontal gyrus.

3.4 Discussion

The present study experimentally induced positive and negative emotions in patients with AHP and HP controls, and measured the resulting changes in motor awareness. It also investigated the brain lesions associated with the clinical diagnosis of AHP, as well as with performance on the experimental task. The main behavioural finding was that patients with AHP showed a significant improvement in motor awareness following a negative, but not a positive, emotion induction. The main finding of the analysis combining experimental and lesion data was that lesions to the putamen, the anterior insula, the capsules and the anterior periventricular white matter were associated with less awareness improvement on the experimental task. These findings are discussed in turn below.

To the authors' knowledge, this is the first experimental demonstration of the role of emotion in AHP. The results show that negative, self-referential emotion induced by social feedback can lead to temporary improvements in motor awareness, in patients who otherwise show stable AHP. These results are consistent with previous clinical observations of transitory awareness improvements and 'catastrophic reactions' following discussions of negative themes such as loss, separation or mortality (Kaplan-Solms & Solms, 2000). They are also consistent with experimental manipulations of perspective-taking, in which taking a 3rd person perspective of one's disability can lead to awareness improvements and increase of depressive emotions (Marcel et al., 2004; Fotopoulou et al., 2009, 2011). It is proposed that these results cannot be accounted for by either the psychodynamic or 'valence' hypothesis (see Introduction, Section 3.1), and instead are best explained by theories that assume 'top-down', emotional abnormalities (Fotopoulou et al., 2010; Turnbull et al., 2005; Vuilleumier, 2004). Moreover, although changes to neglect and unawareness for neglect following emotion induction were tested in only a small subset of patients, it appears that the effects of negative emotion on awareness are specific to motor awareness and do not extend to neglect or its unawareness. These findings and their potential interpretations are in turn discussed below.

While the results could be interpreted as psychodynamic 'lifting' of denial and repression, the psychodynamic hypothesis could just as easily predict the opposite result, namely a defensive, decrease of awareness due to the negative emotions experienced following negative feedback. Thus, the predictions of this theory in relation to the results are not

clear. Similarly, although patients with AHP showed significantly less depressive feelings and symptoms than controls on a self-report measure (see also Fotopoulou et al., 2010), the experimental results could not be accounted for by the ‘valence’ hypothesis. This is because patients with AHP showed greater awareness changes following the negative emotion induction, suggesting that they were able to process such emotions at some level. Indeed, both groups reported feeling more negative emotions following negative versus positive feedback in a ‘manipulation check’ measure. Interestingly, during the experiment, patients with AHP reported feeling overall more positive emotion than control patients, but this effect was unrelated to the valence of the feedback provided. This may relate to the aforementioned, more general tendency of patients with AHP to *report* (rather than experience) less negative emotions (see also Turnbull et al., 2005). Thus, as the patients were able to experience increased negative emotions following the negative emotion induction and increased positive emotions following the positive emotion induction, these results suggest that their emotional difficulties do not consist of a primary deficit in emotional processing (as the valence hypothesis suggests). Instead, as their emotional difficulties seem to relate more specifically to their motor awareness (also see above), they may be suffering from a more specific, higher-order impairment in consciously, self-attributing negative emotions, i.e. attributing negative emotions to at least some of their higher-order self-representations (see also Fotopoulou, 2010; Turnbull et al., 2005, 2014).

This interpretation is also supported by the findings of the lesion mapping analysis. Specifically, the presence (lesion overlay results) and severity (Feinberg VLSM results) of anosognosia were associated with lesions to a range of cortical and subcortical areas previously associated with AHP (Berti et al., 2005; Fotopoulou et al., 2010; Karnath et al., 2005; Moro et al., 2011; Vocat et al., 2010). However, worse performance on the critical condition of the experimental task (i.e. less awareness change following negative feedback) was associated with lesions to the putamen, the anterior insula, the capsules and the anterior periventricular white matter.

The insula, and particularly its anterior sectors, is increasingly identified as the neural substrate for the conscious representations of internal bodily signals (interoception; Critchley et al., 2004; Craig, 2009), as well as for the processing of salience (Seeley et al., 2007). Thus, in patients with AHP, damage to the right insula and related white matter connections may be linked with impoverished interoceptive signals about the left-side of

the body (see also Karnath et al., 2005; Fotopoulou et al., 2010). It is possible to speculate that this deficit may affect how patients process the salience and emotional significance of signals arising in this body side, thus explaining how they can remain in denial of their paralysis and/or apathetic towards the normally alarming sight of a paralysed left arm (Romano, Gandola, Bottini, & Maravita, 2014). Similarly, the functional role of the basal ganglia and particularly the striatum has been associated with prediction error-driven learning (O'Doherty et al., 2003), as well as the aberrant salience theories of psychosis (Gray et al., 1991; Kapur, 2003). In AHP such deficits can be linked with both specific instances of aberrant motor monitoring in functionally specialised systems (Berti et al., 2005), or more generally in global error monitoring, salience processing and belief updating (Davies et al., 2005; Venneri & Shanks, 2004; Vocat et al., 2013). For example, according to a probabilistic, predictive coding theory of AHP (Fotopoulou, 2012; 2014), such lesions could be understood to disrupt neuromodulatory circuits in AHP, leading for example to dopamine-depletion and a difficulty in optimising the precision (uncertainty) of prediction errors (Friston et al., 2012), affecting their salience and, ultimately, the learning of new information. Thus, even when signals about the current state of the body may be available, they may be 'imprecise', and thus unable to update prior beliefs about the self. This ultimately leads to aberrant inferences about one's current abilities and abnormal adherence to past beliefs about the body.

It is thus possible to speculate that in AHP patients who fail to update their emotions and beliefs about their current state of the body (i.e. their left-sided paralysis), the provision of negative feedback by social means can generate negative emotions about the self and new learning on the basis of other intact areas. Future studies will be needed to verify this prediction, perhaps using functional neuroimaging to detect residual emotional processing in AHP patients. In addition, given the potential specificity of the effects (concerning motor but not spatial awareness), future studies should explore the psychological and neural relation between emotional processing and the motor system. Indeed, a growing literature is suggesting a tight interrelation between emotion and motor representations (see Gentsch, & Synofzik, 2014; Pereira et al., 2011). Consistent with the current findings, previous studies have shown that while negative emotional processing competes for attentional resources with visual tasks to the detriment of performance on the latter (Erthal et al., 2005; Hartikainen, Ogawa & Knight, 2000; Tipples & Sharma, 2000), they may enhance processing in motor-related brain areas. Indeed, several studies of non-human primates have found the involvement of motor-related cortical areas during

threatening contexts (e.g., Graziano & Cooke, 2006), while emotional threat has been found to be associated with increased motor cortex excitability in humans (Baumgartner, Willi, & Jäncke, 2007; Hajcak et al., 2007; Oliveri et al., 2003). Induction of fear has been found to modulate activity in primary motor cortex and putamen (Butler et al., 2007; Phelps et al., 2001). These findings have been interpreted in contemporary theories of emotion as consistent with the idea that aversive contexts engage motor circuits in order to prepare participants for action that may protect the organism from threat (Azevedo et al., 2005; Bradley, Codispoti, Cuthbert, & Lang, 2001; Hajcak et al., 2007). The current results may indeed relate to such an enhancement of activity in residual motor-related areas and future, electromyography or neuroimaging studies can specifically test such speculations and predictions.

3.4.1 Limitations

The small sample size and the inherent limitations of the voxel-based lesion-symptom mapping approach (Rorden, 2007; Volle et al., 2011; Geva et al., 2012), only allow for preliminary evidence of the possible neural correlates observed. Nevertheless, the VLSM approach, compared to other lesion analysis methods, does offer several advantages, including the use of continuous scores of behavioural performance instead of the classification of patients into categorical groups. An additional limitation concerns the fact that a ‘neutral emotion’ or ‘no feedback’ control condition was not included in the experiment, which would allow for the comparison of both negative and positive emotion conditions. In addition, it was not possible to control for floor effects in the control group given the unique nature of anosognosia. Nevertheless, although there was a smaller margin for change in awareness scores for the control group, there was still a small change evident in the same direction as the AHP group. Furthermore, this control group allow for the control for other more basic confounding effects such as age, test adherence, cognitive functioning, practice, repetition, comprehension and fatigue effects.

Importantly, the observed changes were temporary and generated under specific experimental conditions, and thus the results of the experiment are not directly relevant to clinical studies. However, these findings do have indirect implications for clinical work; they reinforce the previously demonstrated link between awareness improvement and depressive feelings, as well as more generally emphasise the role of emotion in the syndrome, despite some patients’ apparent lack of emotional reactivity.

Chapter 4 Mentalising the body: spatial and social cognition in anosognosia for hemiplegia

4.1 Introduction

In cognitive neurology and neuroscience, the ability to integrate multimodal sensorimotor signals into an egocentric reference frame and assign a 1st person perspective to one's bodily experiences has long been recognised as the sine qua non of human self-consciousness (Blanke et al., 2002; Vogeley et al., 2001, 2004). By contrast, the cognitive ability to disengage from the 1st perspective and to adopt another person's visuospatial and mental perspective is considered as a fundamental prerequisite for the metacognitive ability to understand and infer the thoughts and feelings of others, the so called 'theory of mind' (ToM), or 'mentalisation' abilities (Frith & Frith, 2007). In recent decades, both of these research traditions, namely 1st person, embodied cognition and 3rd person, social cognition have received ample, empirical attention. Yet far less neuroscientific studies have focused on the importance of the 3rd person perspective on our bodily self.

In fact, most of the existing studies in cognitive neurology and neuroscience that have investigated the ability to mentally disengage from the 1st person, embodied perspective have focused on how we 'project' our psychological selves to other positions in space (Blanke, Landis, Spinelli, & Seeck, 2004), or to other bodies (Sinigaglia, 2012). For example, Blanke and colleagues investigated the underlying neural mechanisms of out-of-body experience (i.e. to see one's body and the world from a location outside one's physical body while awake) and autoscopia (i.e. seeing one's body outside extrapersonal space), showing that they share important key mechanisms, such as proprioceptive, tactile, visual and vestibular sensations, and neuroanatomical damage around the temporal parietal junction. Yet still the question of how we perceive the self *from* such disembodied perspectives has not been investigated. This is an important question as developmental, clinical and social psychology have long established that how we perceive or, imagine the self to be from the perspective of other people (e.g. as in physical mirrors, or during social mirroring) is critical for the development and maintenance of a coherent and resilient self that entails the integration of 1st and 3rd person perspectives (Rochat, 2009). In fact, severe mismatches between 1st person perspectives and 3rd person objectifications of one's bodily self seem to underlie symptom formation in several psychopathologies, such as eating disorders and schizophrenia (Langdon & Coltheart, 2001; Russell, Schmidt, Doherty, Young, & Tchanturia, 2009). There is also now

increased understanding of the relation between self-awareness difficulties and mentalisation impairments in these disorders (Langdon, Corner, McLaren, Ward, & Coltheart, 2006; Russell et al., 2009; Tchanturia et al., 2004).

More generally, while the interaction and the potential overlap of networks that support self-referent processing and social cognition in the brain has been long recognised (see Lieberman, 2007; Uddin, Iacoboni, Lange & Keenan, 2007, for reviews) the precise ways in which such systems interact to influence self-awareness remains to be understood. For example, distinctions have been recently proposed between a network of ‘cortical midline structures’, responsible for internally oriented processes that support reflections on one's own or others’ mental states versus an externally focused, lateral frontoparietal network that responds to one's own or others’ visible features and actions (Lieberman, 2007). Another view is to consider the right frontoparietal system involved in representing the bodily self and other, versus a cortical midline system involved in representing self and other in more reflective terms (Uddin et al., 2007). Despite the rich debates surrounding such proposals and the many functional neuroimaging studies conducted in healthy participants, the question of how taking a 3rd person perspective on the self may influence bodily self-awareness remains beyond the scope of these studies.

In this respect, neurological disorders of bodily awareness can offer an additional window of insight into the complicated relation between self-awareness and social cognition. In particular, this study aimed to investigate the relation between bodily, self-awareness and social cognition in a prototypical neurological disorder of the bodily self, anosognosia for hemiplegia (AHP). Interestingly, patients with AHP typically remain anosognosic when they view their paralysed limbs from a 1st person perspective, as when their plegic arm is brought into the ipsilateral visual field and its paralysis is demonstrated by the examiner (Bisiach et al., 1986). They also remain anosognosic during conventional ‘mirror therapy’ (where a mirror is placed perpendicular to the body and the intact arm appears in the expected position of the paralysed arm, e.g. Ramachandran, 1995; Zampini, Moro, & Aglioti, 2004), or when 1st person, visual feedback of the paralysis is provided by realistic rubber hands (Fotopoulou, et al., 2008).

By contrast, it has been shown that patients show dramatic improvements in body recognition and awareness when they are provided with visual feedback of their own body in the 3rd person perspective, i.e. when visual feedback of their paralysis is provided

via mirrors or video replays (Fotopoulou et al., 2009; Fotopoulou et al., 2011; Jenkinson et al., 2013; also see Chapter 6). Similarly, patients show more awareness of their paralyses when asked to make verbal judgments from 3rd person perspectives (Marcel et al., 2004; Fotopoulou et al., 2011). These findings suggest that 3rd person, visual spatial perspectives as well as more abstract, 3rd person, verbal representations of the self may be intact in these patients, in the sense that they can perceive the current state of the body accurately from such perspectives. However, these results leave open the question of why patients do not habitually use such 3rd person perspectives and knowledge to inform and update their 1st person perspective on their bodily state. One possibility (Fotopoulou, 2014) is that they have lost the cognitive ability to do so without explicit, experimental instructions, or manipulations, i.e. they are not as able as healthy individuals to spontaneously disengage from the 1st person perspective and take 3rd person visual spatial or, mental perspectives more generally.

This possibility, which we tested in the present study, is also consistent with some of the lesion sites selectively associated with AHP in recent studies. Specifically, among the critical cortical areas (e.g., inferior and middle frontal gyrus, insula, superior temporal gyrus; STG; temporo-parietal junction; TPJ) that have been selectively associated with AHP (Berti et al., 2005; Fotopoulou et al., 2010; Karnath et al., 2005; Moro et al., 2011; Vocat et al., 2010; also see Chapter 3). Areas such as the STG and the TPJ have also been implicated in the so-called “mentalising network” (Aichhorn et al., 2009; Gallagher & Frith, 2003; Koster-Hale & Saxe, 2013; Siegal & Varley, 2002), while damage to areas around the right inferior and middle frontal gyri have been shown to relate to a difficulty to inhibit the self-perspective (Samson, Apperly, Kathirgamanathan, & Humphreys, 2005). Nevertheless, to the authors knowledge no behavioural, nor neuroimaging study has examined the relationship between AHP and social cognition. This was the aim of the current study.

Specifically, this study aimed to examine both visual-spatial perspective-taking and reflective (verbal) facets of mentalising in a group of patients with right-hemisphere damage and severe AHP, compared to a control group of patients with right-hemisphere damage but no AHP, and a second, control group of neurologically healthy participants. To this end, a visual-spatial perspective taking experiment was designed and tested, as well as a set of ‘theory of mind’ stories that required participants to infer the mental states of agents in each story presented from different perspectives. Based on the hypothesis that

AHP patients may be unable to spontaneously take 3rd person perspectives and use such information to update their self-awareness (see above), it is expected that they would perform worse than both control groups in the 3rd person conditions on both tasks. It was also expected that such deficits would be associated with their degree of motor unawareness, as well as with some executive functions impairments. A secondary prediction was that both right-hemisphere groups would perform worse than healthy controls on both tasks, consistently with the aforementioned previous studies.

Finally, advanced lesion mapping methods such as voxel-based lesion symptom mapping (VLSM; Bates et al, 2003; Rorden et al., 2007) was used to identify the areas commonly damaged in patients, and the relation of the damaged brain areas to the behavioural scores in the experimental tasks. It is predicted that lesions of the inferior and middle frontal gyrus (IFG and MFG), the supramarginal gyrus (i.e. TPJ) and the STG would be linked with worse performance on the experimental tasks, with the last two areas being implicated more in visual spatial versus verbal perspective-taking, respectively.

4.2 General Methods

4.2.1 Participants

Thirty right-handed, adult neurological patients with right-hemisphere lesions and contralateral hemiplegia (16 females, mean age = 68.44 years, SD = 12.73 years) participated in the study. Patients were recruited from consecutive admissions to three acute stroke wards using the inclusion criteria specified in Chapter 2.

Patients were divided into two groups based on their clinical diagnosis of AHP. This classification was based on the Berti structured interview (Berti et al., 1996) and the Feinberg et al. (2000) scale as described in Chapter 2. Based on the Berti interview, fifteen patients were classified as having AHP (AHP; 9 females, mean age = 66.53 years, SD = 13.67 years, age range: 47-88 years) and 15 patients were classified as hemiplegic controls (HP; 7 females, mean age = 67.13 years, SD = 16.02 years, age range: 36-86 years). This classification was then further confirmed by the Feinberg scale. Patient performance on the experimental tasks was compared to 15 age-matched healthy (non-neurological) controls recruited at the same hospital sites, among visitors to the hospital wards (HC; 6 females, mean = 71.67 years, SD = 6.98, age range: 60-90).

4.2.2 Neurological and neuropsychological assessment

In addition to the above anosognosia assessments, the neurological and neuropsychological profile of the patients was formally assessed using selective measures specified in Chapter 2. Specifically: motor strength of upper and lower limbs was assessed; proprioception as well as visual fields and tactile extinction tested; orientation, working memory and mood, as well as visual-spatial, representational and personal neglect were assessed. Patients, as well as healthy controls, were additionally assessed using the following neuropsychological measures detailed in Chapter 2: general cognitive functioning together with long-term verbal recall were assessed; premorbid intelligence and executive and reasoning abilities were tested.

4.3 Experimental investigations

4.3.1 Experiment 1: Visual-spatial perspective taking (VSPT)

4.3.1.1 Design

In order to assess visual-spatial perspective taking (VSPT), a visual-spatial task was designed that required participants to count the number of items observed from different visual-spatial perspectives (see task details below). A 3 x 3 design was used with one between-subject factor (Group: AHP vs. HP vs. HC) and one within-subject factor (Perspective: 1st PPT vs. 3rd PPT animate vs. 3rd PPT inanimate). The main dependent variable was the total number of correct responses. Each trial was binary scored (1 = correct, 0 = incorrect). Total scores were converted into percentages for statistical analyses (see below).

4.3.1.2 Materials and procedures

To construct a suitable VSPT task for the patient populations, an existing task was adapted and piloted (Langdon & Coltheart, 2001; Samson et al., 2005). The task (see Figure 4.1 for an illustration) involved three visual-spatial positions and corresponding perspectives: (1) the participant seated at his/her wheelchair in front of a table (1st person perspective), (2) the experimenter seated directly opposite the participant (at a 180° angle; 3rd person animate perspective) and (3) a photo-camera (placed on a table at the right-hand side of the patient to account for left visuospatial neglect) at a 90° angle (3rd person inanimate perspective). Six transparent plastic cups were placed on a tray, which was

placed at the centre of the table. The participants were asked four types of questions about the cups presented in a pseudo-random order:

- (a) *Physical property judgment (quantity), control questions*: “How many cups are there on the tray?”; “How many cups do you see on the tray?”; and “If the camera took a picture, in the picture, how many cups would be seen on the tray?”
- (b) *1st person perspective*: “How many cups do *YOU* see in the front row?”
- (c) *3rd person animate perspective*: “How many cups do *I* see in the front row?”
- (d) *3rd person inanimate perspective*: “If the *CAMERA* took a *picture*, in the *PICTURE*, how many cups would be seen in the front row?”

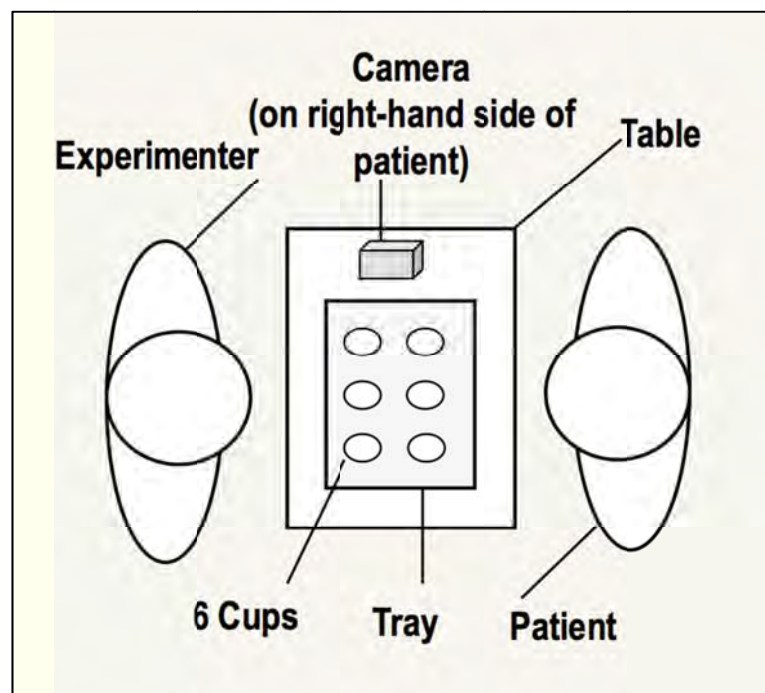


Figure 4.1 Schematic representation of the visual-spatial perspective taking task

Note: The experimenter sits directly in front of the participant (180° shift in perspective) and the camera on the right-hand side (90° shift in perspective); the position of the cups on the tray is changed from trial to trial, with the participant being asked how the himself/herself (1st person perspective), the experimenter (3rd person animate perspective), or the camera (3rd person inanimate perspective) would see the display.

The position of the cups on the tray was changed after each trial, with the number of cups in the “front row” differing for each visual-spatial perspective (the participant, the experimenter and the camera). Five different arrangements were used (see Appendix I) for examples): two were used for the physical property control trials and three different arrangements were used for the VSPT trials. In total, the task consisted of six control trials and six VSPT trials (two per perspective condition).

Example items and questions controlling for visual-spatial neglect (for patients only) preceded the experimental questions (see Appendix J). The experiment only proceeded if the participant could see the tray and count all cups during all practice items and at regular intervals between conditions. Results from the pilot study confirmed that experimental instructions were fully comprehensible and patients’ performance was not influenced by neglect.

4.3.2 Experiment 2: Theory of mind (ToM) stories

4.3.2.1 Design

In order to assess verbal ToM abilities, previous story-based tests were adapted (Hynes et al., 2006) that required participants to understand the mental states (e.g., beliefs, intentions or emotions) of different people in the stories. The experimental design included one between-subject factor (Group: AHP vs. HP vs. HC) and two within-subject factors (Perspective: 1st PPT vs. 3rd PPT; and Order: 1st order vs. 2nd order). Perspective was manipulated by changing the ‘person’ in which the protagonist of the stories was presented. First person perspective stories were expressed in the 2nd person (e.g. “You are sitting by the TV...”), while 3rd person perspective stories were expressed in the 3rd person (e.g. “Eddie is sitting by the TV ...”). Order was manipulated by altering the questions participants were required to answer so that the participants had to understand a character’s mental state (1st order) or a character’s belief about the mental state of another character in the story (2nd order). This design allowed for a 3 x 2 x 2 comparison on the main dependent variable of ToM accuracy, which comprised of a composite score of spontaneous and multiple-choice answers (minimum score = 0; maximum score = 2). However, supplementary statistical analysis were also run using multiple-choice answers only, showing the same pattern of results.

4.3.2.2 Materials and procedures

Twenty stories were created in total: sixteen target ToM stories and four control stories, of carefully matched characteristics. All stories consisted of at least two characters and were followed first by an open ToM question and then by three multiple-choice responses (Hynes et al., 2006). Ten of the stories (eight ToM and two control) were expressed in the 1st person, while the other ten were expressed in the 3rd person (see Figure 4.2, and examples in Appendix K). Half of the ToM stories were followed by a question about the mental state of one of the character's (1st Order), while the other half consisted of an extension of the original story and were followed by a question about the beliefs of one of the characters about the mental states of the other character (2nd Order). The control stories were similar to the ToM stories and involved social situations, but the questions required inferential reasoning and semantic knowledge rather than perspective taking. ToM and control stories in both conditions did not differ in word length ($t(18) = 0.46, p = 0.87$; mean = 112 words in length).

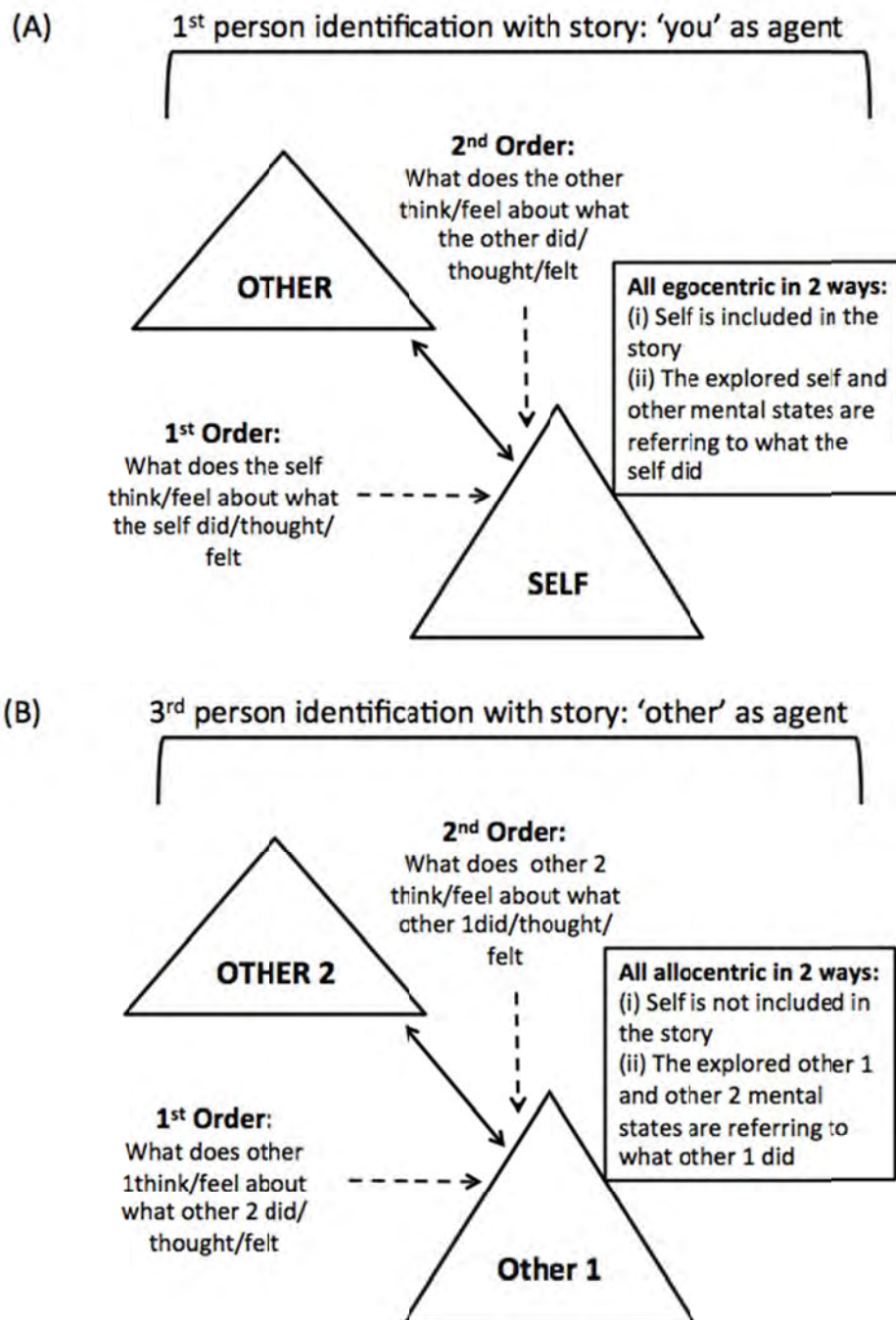


Figure 4.2 Figure representing 1st person and 3rd person perspective taking sets of ToM stories

Note: **A.** 1st person perspective-taking stories depicting the 2 actors (self and other) with “you” as the agent. Questions are expressed in the 2nd person and are egocentric (the self related to the other); the dotted arrows represent the 1st order and 2nd order levels. **B.** 3rd person perspective-taking questions depicting the 2 actors (other 1 and other 2) with the “other” as the agent. Questions expressed in the 3rd person and are allocentric (the other unrelated to the self); the dotted arrows represent the 1st order and 2nd order levels.

Procedures

All scenarios and questions were read out-loud to the participants, in slow pace and neutral tone. Stories and questions were repeated on request of the participant or if the examiner felt it was necessary due to distraction or fatigue reasons. Participants were self-paced and were given ample time for responding. The participants were first required to make a spontaneous response, which the examiner wrote down in full. Subsequently, the experimenter read the multiple-choice options and participants had to indicate their choice verbally, which all patients were able to do. Of the multiple-choice options given, there was only one possible correct answer, the other options being either (i) the incorrect belief or (ii) irrelevant or incoherent with the story. For each question a composite score was calculated using both the multiple-choice answers and the spontaneous answer. Multiple-choice answers were scored as 1 = correct and 0 = incorrect. Spontaneous answers were scored as 1 = correct, 0.5 = partially correct/inadequate and 0 = incorrect. Two raters scored the spontaneous answers independently. Interclass correlation coefficient of 0.95 indicated a good agreement between raters. Divergent scores (<1% of stories) were discussed and jointly agreed on. Total scores were converted into percentages and used in the statistical analyses.

In the patient groups, testing was conducted in two successive sessions to avoid fatigue. The order of the presentation of the two sets (1st PPT and 3rd PPT) was counterbalanced. Each set began and ended with a control story. To check for comprehension, following each control story, all participants were asked to rate how well they understood the story. A 5-point Likert-type scale was used (i.e. “Using this scale from one to five, how well did you understand the story? One being the lowest score, where you understood very little, and 5 being the highest score, where you understood the whole story”). The scale was read aloud to participants and also presented visually as a vertical scale on an A4 sheet of paper (from one to five), positioned in the right visual field in order to minimise possible unilateral visual neglect effects in the patient groups. Participants were familiarised with the rating scale before the experiment. The task was piloted on twenty healthy controls and four neurological patients (two AHP and two HP) to test for comprehension of stories and questions, possible attentional biases in the patient group and other testing considerations. The results confirmed the suitability of the stories and questions but minor corrections were made on the readability of the specific stories.

4.3.3 Control experiments

4.3.3.1 Control false belief tasks

Two classic false belief tasks were used as a baseline measure of the participants' ability to understand that others may have representations of the world that are false and/or different from their own (Baron-Cohen, Leslie & Frith, 1985). Task 1 was an age-adapted version of the "Smarties" task (Gopnik & Astington, 1988). It involved a direct, 1st person scenario, where the participant is directly involved in the scenario by participating as an active agent. Baron-Cohen et al.'s (1985) "Sally-Anne" false belief task was used as the second task. Task 2 involved an indirect, 3rd person scenario, where the participant is not directly involved and is read a narrative about other agents (see Appendix L for full description of methods).

4.3.3.2 Mental rotation task

A mental rotation task (Vandenberg & Kuse, 1978; Neuburger et al., 2011) was added as an additional control task to assess whether deficits in visual-spatial perspective could be attributed to impairments in mental rotation ability. This was tested on a subset of patients (six AHP and HP patients, respectively). The mental rotation task involves two conditions: a letter condition where a picture of the letter "F" is used and an animal condition where a line drawing of an elephant is used. The patient is required to mentally rotate the stimuli in each condition. In each condition, the target stimulus is shown on the right-hand side and four comparison stimuli are also presented vertically on the right side. The comparison stimuli are presented using two of five possible rotation angles across both conditions: 90°, 135°, 225°, 270° and 315°. Two of the four comparison stimuli are correct (i.e. actual rotations of the target image) and two incorrect (left-right reversed mirror images of the target, rather than an angular rotation). The patient is asked to cross out the two correct comparisons. The order of presentation of the two conditions was counterbalanced.

4.3.4 Statistical analysis

All behavioural analyses were conducted in SPSS (IBM Corp, 2013.). Non-parametric tests were used as the data were not normally distributed. For analysis of neurological and neuropsychological tests, the alpha significance level was set to $\alpha = 0.01$ to account for multiple comparisons. For the experimental tasks, Bonferroni corrections were used where appropriate.

Furthermore, the pattern of correlations was examined between perspective taking and (1) frontal inhibition (i.e. go-no-go task from the FAB), as well as (2) anosognosia (using the Feinberg awareness scores) and perspective taking (3rd person condition scores in both the VSPT and the ToM tasks) in the AHP group. Non-parametric Spearman's rho tests were used for all correlation analyses.

4.3.5 Lesion mapping methods

Routinely acquired clinical scans (CT and/or MRI) were obtained for 29 patients (clinical data set of one HP patient was unavailable) within the first week of symptom onset. Lesion mapping methods specified in Chapter 2 were followed for analysis below. Separate VLSM analyses were run for the following dependent variable (continuous scores): i) Feinberg awareness scores, ii) 3rd PPT scores in the visual-spatial tasks, and iii) 3rd PPT in ToM stories. For these behavioural measures, a lower score corresponded to lower awareness and lower perspective taking ability in both the VSPT and ToM tasks. For the purpose of this paper the term temporal-parietal junction (TPJ) refers to the area centered around the supramarginal and angular gyrus at the convergence of the superior temporal lobe and the inferior parietal lobe.

4.4 Results

4.4.1 Demographic and neuropsychological results

A summary of the neuropsychological and neurological profile of the participants is provided in Table 1.1. No significant difference was observed for age, years of education, pre-morbid IQ, long-term memory recall and general cognitive functioning between all three groups (all p 's > 0.15). As expected, there was a significant difference in awareness scores (Berti interview: $Z = -4.99$, $p < 0.001$; Feinberg scale: $Z = -4.83$, $p < 0.001$) between the patient groups (AHP vs. HP). The patient groups did not differ in their time of symptom onset and assessment interval, orientation, or working memory (p 's > 0.53). The scores of both patient groups were also within the normal range for the general Hospital Anxiety and Depression Scale. AHP patients performed significantly worse on tests of proprioception compared with HP patients ($Z = -3.17$, $p < 0.001$). Both patient groups presented with similar visual and sensory deficits, as well as visual-spatial and personal neglect. Neglect appeared to be more impaired in the AHP group, although such differences did not reach significant levels as set ($\alpha = 0.01$; e.g., star cancellation: $Z = -2.46$, $p = 0.013$; Comb/Razor test of personal neglect percent bias: $Z = -1.96$, $p = 0.08$).

Both patient groups performed outside the normal range on the Cognitive Estimates Test suggesting possible deficits in abstract reasoning, however, there was no statistical difference between groups (AHP vs. HP; $Z = -0.04$, $p = 0.98$). There was a significant difference between patient groups on FAB scores, with AHP patients performing significantly worse overall ($Z = -3.05$, $p < 0.001$), and on three subtests, specifically: conflicting instructions ($Z = -3.25$, $p = 0.001$), inhibitory control (go-no-go test; $Z = -4.04$, $p < 0.001$), and precision behaviour ($Z = -3.17$, $p = 0.002$). The healthy controls scored within the normal range.

Table 4.1 *Groups' demographic and neuropsychological profile*

| | AHP | | HP | | HC | | Mann-whitney | | Kruskal Wallis | |
|-------------------------------|-------------------|-------|----------------|-------|--------|------|--------------|---------|----------------|---------|
| | Median | IQR | Median | IQR | Median | IQR | Z | p | X ² | p |
| N | - | - | - | - | - | - | - | - | - | - |
| Age (years) | 73.00 | 22.00 | 68.00 | 27.00 | 71.00 | 7.00 | -0.15 | 0.89 | 0.75 | 0.69 |
| Education (years) | 12.00 | 3.00 | 12.00 | 3.00 | 13.00 | 6.00 | -0.57 | 0.58 | 3.16 | 0.21 |
| Days from onset | 8.00 | 12.00 | 9.00 | 7.00 | - | - | -0.08 | 0.94 | - | - |
| MRC Left upper limb | 0.00 | 0.00 | 0.00 | 0.00 | - | - | -0.54 | 1.00 | - | - |
| MRC left lower limb | 0.00 | 1.25 | 1.00 | 2.00 | - | - | -0.53 | 0.68 | - | - |
| Premorbid IQ-WTAR | 40.00 | 17.50 | 32.00 | 12.00 | 48.00 | 4.75 | -0.04 | 0.98 | 8.01 | 0.02 |
| Berti awareness interview | 2 ^a | 1.00 | 0.00 | 0.00 | - | - | -4.99 | <0.001* | - | - |
| Feinberg awareness scale | 6 ^a | 4.00 | 0.00 | 0.00 | - | - | -4.83 | <0.001* | - | - |
| Orientation | 3.00 | 0.00 | 3.00 | 0.00 | - | - | -1.39 | 0.52 | - | - |
| Digit span forwards | 6.00 | 2.00 | 6.00 | 2.00 | - | - | -0.30 | 0.78 | - | - |
| Digit span backwards | 3.00 | 2.00 | 2.00 | 2.50 | - | - | -0.62 | 0.53 | - | - |
| MOCA memory | 3.50 | 2.00 | 5.00 | 1.00 | - | - | -1.13 | 0.31 | 0.99 | 0.32 |
| MOCA | 24.00 | 9.25 | 25.00 | 4.50 | - | - | -0.99 | 0.36 | 2.58 | 0.95 |
| Visual fields | 3.5 ^a | 2.25 | 2 ^a | 4.00 | - | - | -0.68 | 0.52 | - | - |
| Somatosensory (max 6) | 3 ^a | 2.00 | 2 ^a | 1.50 | - | - | -1.84 | 0.08 | - | - |
| Proprioception (max 9) | 4.00 | 3.00 | 7.00 | 1.00 | - | - | -3.17 | <0.001* | - | - |
| Comb/razor test bias | -0.44 | -0.32 | -0.23 | -0.38 | - | - | -1.96 | 0.08 | - | - |
| Comb/razor test left | 3.00 | 3.50 | 7.50 | 4.75 | - | - | -3.13 | 0.007* | - | - |
| Comb/razor test right | 11.00 | 4.25 | 10.50 | 5.55 | - | - | -0.36 | 0.73 | - | - |
| Comb/razor test ambiguous | 4.50 | 3.25 | 4.00 | 4.25 | - | - | -0.58 | 0.58 | - | - |
| Bisiach one item test (max 3) | 1.00 | 1.25 | 1.00 | 1.00 | - | - | -1.03 | 0.38 | - | - |
| Star cancellation | 12.5 ^a | 7.50 | 40.00 | 35.50 | - | - | -2.46 | 0.013 | - | - |
| Line bisection | 0 ^a | 2.25 | 2.00 | 2.00 | - | - | -2.08 | 0.04 | - | - |
| Copy | 0 ^a | 0.25 | 1 ^a | 1.00 | - | - | -1.94 | 0.06 | - | - |
| Representational drawing | 0.00 | 0.25 | 1.00 | 1.00 | - | - | -2.40 | 0.03 | - | - |
| Cognitive estimates | 9 ^a | 7.75 | 8 ^a | 7.00 | 6.50 | 5.75 | -0.04 | 0.98 | 3.71 | 0.16 |
| FAB total score | 10.00 | 4.00 | 15.00 | 3.50 | 16.00 | 3.00 | -3.05 | <0.001* | 21.18 | <0.001* |
| Similarities | 2.00 | 1.00 | 2.00 | 0.00 | 2.00 | 1.00 | -2.02 | 0.05 | 8.78 | 0.01 |
| LexialFluency | 2.00 | 1.00 | 3.00 | 1.00 | 3.00 | 1.00 | -2.19 | 0.02 | 8.27 | 0.02 |
| MotorSeries | 2.00 | 1.00 | 3.00 | 1.50 | 3.00 | 1.00 | -1.35 | 0.20 | 4.07 | 0.13 |
| ConflictIns | 2.00 | 1.00 | 3.00 | 0.25 | 3.00 | 1.00 | -3.25 | 0.001* | 16.47 | <0.001* |
| GonoGo | 0.00 | 1.00 | 3.00 | 1.00 | 2.00 | 1.00 | -4.04 | <0.001* | 22.69 | <0.001* |
| PresBehav | 2.00 | 1.00 | 3.00 | 0.00 | 3.00 | 0.00 | -3.17 | 0.002* | 17.77 | <0.001* |
| HADS depression | 6.00 | 6.25 | 7.00 | 6.50 | - | - | -1.37 | 0.18 | - | - |
| HADS anxiety | 7.00 | 6.25 | 7.00 | 9.00 | - | - | -0.37 | 0.73 | - | - |

Medical Research Council (Guarantors of Brain, 1986); MOCA=The Montreal Cognitive Assessment (Nasreddine, 2005); Comb/razor test = tests of personal neglect (McIntoch et al., 2000); Bisiach one item test= test of personal neglect; Visual fields and somatosensory= customary 'confrontation' technique= Bisiach et al. (1986); line crossing, star cancellation, copy & representational drawing= conventional sub-tests of Behavioural Inattention Test (Wilson et al., 1987); FAB= Frontal Assessment Battery (Dubois et al., 2000); HADS=Hospital Anxiety and Depression scale (Zigmond, & Snaith,1983)

^a Scores below tests' cut-off points, or more than 1 SD below average mean.

*Significant difference between groups, $p<0.05$

4.4.2 Experimental results

4.4.2.1 Experiment 1: VSPT task

Main effects

All participants answered the control questions correctly without any exceptions. An independent sample Kruskal-Wallis test confirmed a significant main effect of Group ($H(2) = 31.92, p < 0.001, r = 0.73$). Subsequent pairwise comparisons, with Bonferroni corrections ($\alpha = 0.017$) showed significant poorer performance in the AHP group (median = 33.3) compared with both HP patients (median = 83.3; $Z = -3.95, p < 0.001, r = 0.72$), and HCs (median = 100; $Z = -4.87, p < 0.001, r = 0.89$), as well as poorer performance in the HP group relative to HCs ($Z = 2.90, p = 0.004, r = 0.53$).

A Friedman test revealed a significant main effect of Perspective ($\chi^2(2) = 42.99, p < 0.001, r = 0.97$). Pairwise analysis with Bonferroni corrections ($\alpha = 0.017$) showed a significant difference between 1st (median = 100) and 3rd animate conditions (median = 50; $Z = 3.40, p = 0.001, r = 0.5$) as well as the 1st and 3rd inanimate conditions (median = 50; $Z = 4.33, p < 0.001, r = 0.65$). However, there was no significant difference between 3rd animate and 3rd inanimate PPT ($Z = 0.928, p = 0.35, r = 0.14$), as well as no significant difference within groups for 3rd animate and 3rd inanimate PPT ($ps > 0.32$). Therefore the 3rd animate and 3rd inanimate conditions were combined to create a composite score for 3rd PPT (median = 75) and used in subsequent analyses below (see Appendix M).

Two-way effects

The interaction between Group and Perspective was analysed by calculating the difference between 1st PPT and 3rd PPT scores and comparing these between groups using a Kruskal-Wallis test, showing a significant interaction ($H(2) = 27.88, p < 0.001, r = 0.63$). Pairwise comparisons, using Bonferroni corrections ($\alpha = 0.017$) showed no significant difference in 1st PPT abilities between AHP (median = 100) and HP patients (median = 100; $Z = -0.92, p = 0.6, r = 0.16$), the AHP and HC groups ($Z = -1.43, p = 0.48, r = 0.27$), as well as the HP controls and HC's (median = 100; $Z = -1, p = 1, r = 0.18$). However, there was a significant difference in 3rd PPT between both the AHP and HP group ($Z = -3.97, p < 0.001, r = 0.72$), AHP and HC group ($Z = 4.88, p < 0.001, r = 0.89$), as well as between the two control groups ($Z = -2.91, p = 0.004, r = 0.53$). AHP patients (median = 0) therefore present with a specific impairment in 3rd person visual-

spatial PT when compared with both HP control patients (median =75) and healthy controls (median = 100; Figure 4.3). In most cases (i.e. 13 for the 15 patients in both trials) the AHP patients responded with egocentric errors (i.e. responded using their own vantage point, 1PPT, regardless of the visual-spatial perspective required by the question). In some cases, AHP patients expressed frustration with the task because they failed to appreciate the different viewpoints, e.g. “*I don’t see the point in any of this! These questions are too easy.*” or “*Why are you patronising me with such simple questions?*”.

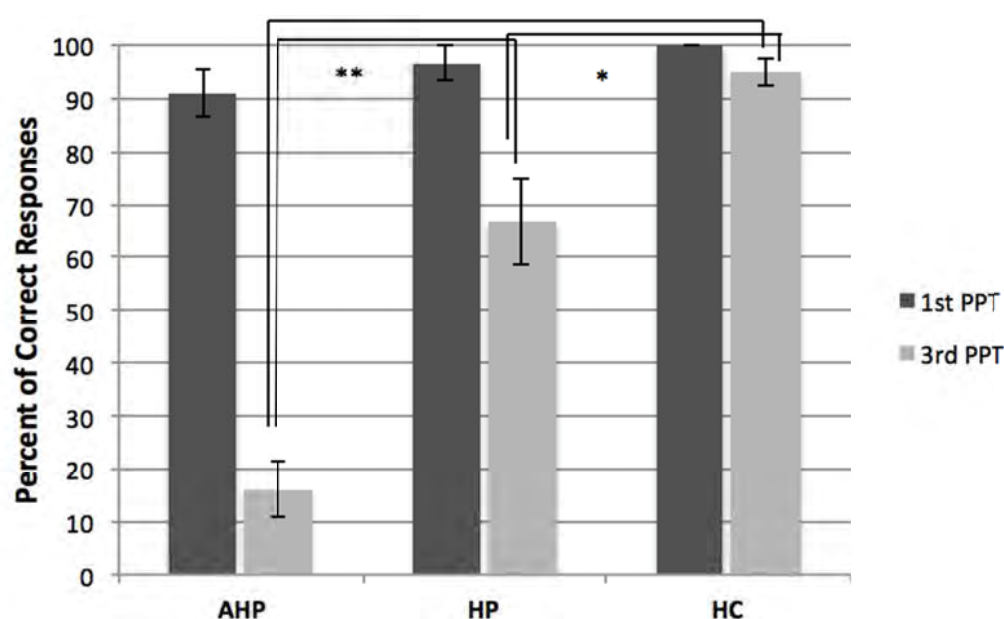


Figure 4.3 *Percentage of correct responses for visual-spatial perspective taking (VSPT) across groups*

Note: Means and SE’s for 1st PPT and 3rd PPT (3rd animate and 3rd inanimate) conditions. AHP patients present with a specific impairment in 3rd PPT, with was no significant difference for 1st person PPT between the AHP and controls groups, but with significant differences in 3rd PPT between the AHP patients and controls.

4.4.2.2 Experiment 2

Control condition and comprehension ratings

All participants performed close to the ceiling level for physical control stories with AHP patients passing 97.5%, HP patient passing 98.33% and HCs passing 99.65% of the questions, respectively. There was no significant difference between groups ($H(2) = 4.96$, $p = 0.1$, $r = 0.1$). All participants reported comprehension ratings between four and five.

Main effects

An independent sample Kruskal-Wallis test confirmed a significant main effect of Group ($H(2) = 20.65, p < 0.001, r = 0.47$). Pairwise comparisons with Bonferroni corrections ($\alpha = 0.017$) showed a significant difference between the AHP and HP groups ($Z = -3.3, p = 0.001, r = 0.6$), AHP and HC group ($Z = -3.94, p = 0.001, r = 0.72$), and HP and HC groups ($Z = -2.34, p = 0.02, r = 0.42$). Therefore overall, the AHP patients (median = 56.25) performed worse on the social stories when compared to HP patients (median = 75) and healthy controls (median = 89.06). A Wilcoxon signed rank test showed a significant main effect of Perspective ($Z = 3.92, p < 0.001, r = 0.58$) with participants performing significantly worse on 3rd PPT (median = 68.75) than 1st PPT questions (median = 81.25). The main effect of Order was also significant ($Z = -5.23, p < 0.001, r = 0.82$), with participants performing significantly worse on 2nd order questions (median = 59.38) compared to 1st order (median = 84.38).

Two- and three-way interactions

The interaction between Group and Perspective was analysed by calculating the difference between 1st PPT and 3rd PPT scores and comparing these between groups. A Kruskal-Wallis test revealed a significant interaction ($H(2) = 22.73, p < 0.001, r = 0.52$). Pairwise comparisons with Bonferroni corrections ($\alpha = 0.017$) showed no significant difference in 1st PPT responses between AHP (median = 81.25) and HP patients (median = 78.5; $Z = 0.23, p = 0.82, r = 0.04$), AHP and HC groups (median = 87.5; $Z = 1.44, p = 0.16, r = 0.23$) as well as HP and HCs ($Z = 1.73, p = 0.85, r = 0.32$). However, there was a significant difference in 3rd PPT between both the AHP and HP group ($Z = 4.34, p < 0.001, r = 0.79$), the AHP and HC group ($Z = 4.2, p < 0.001, r = 0.72$), as well as between the two control groups ($Z = 2.7, p = 0.006, r = 0.49$). AHP patients (median = 31.25) therefore present with a specific impairment in 3rd PPT in ToM stories when compared with both HP patients (median = 68.75) and healthy controls (median = 87.5; Figure 4.4).

The interaction between Group and Order, as well as the interaction between Perspective and Order was likewise analysed by calculating their relevant differential scores and comparing their difference using a Kruskal-Wallis test and Wilcoxon signed rank test respectively. Both interactions were not significant ($H(2) = 2.39, p = 0.30, r = 0.05; Z = -0.94, p = 0.35, r = 0.14$). The interaction between Group, Perspective and Order was analysed by calculating the difference between 1st and 2nd order in the 1st PPT condition

and the 3rd PPT separately, and calculating their difference, and subsequently analysing the effect of Group on this difference using a Kruskal-Wallis test. This interaction was not significant ($H(2) = 0.91, p = 0.63, r = 0.15$).

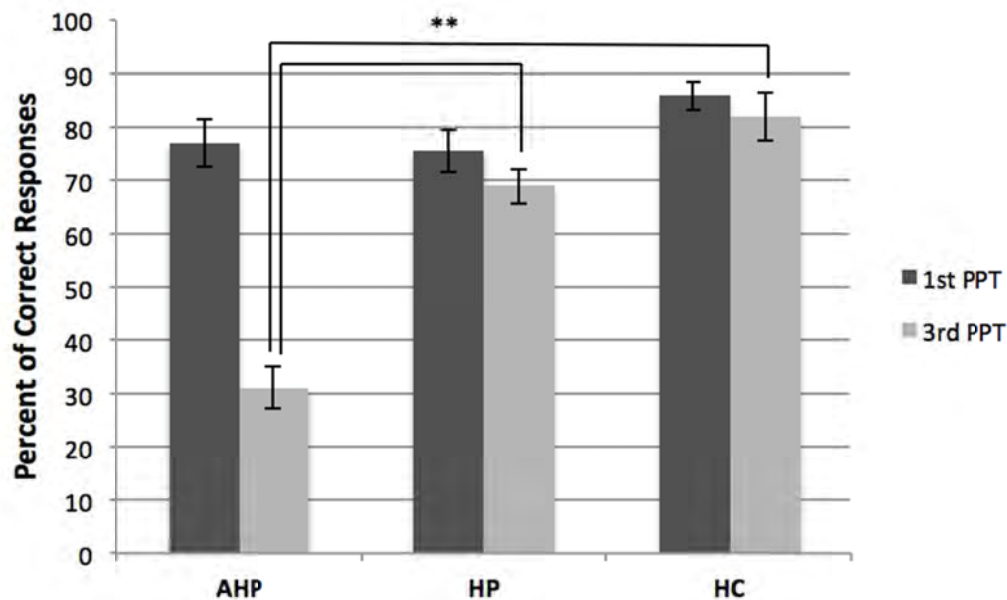


Figure 4.4 *Percentage of correct responses for Theory of Mind stories (ToM) across groups*

Note: Means and SE's for 1st PPT and 3rd PPT conditions. There is no significant difference in 1st PPT between the AHP patients and controls. However, there is a significant difference in 3PPT between the AHP patient and HP patients, as well as healthy controls.

4.4.2.3 Correlations between neuropsychological results and behavioural results

Clinical unawareness and perspective taking

In the VSPT task, there was no significant relationship between the 3rd PPT and Feinberg awareness scores ($r_s(13) = 0.17, p = 0.53$) in the AHP group. In the ToM task there was a significant negative correlation between 3rd PPT and Feinberg awareness scores ($r_s(13) = -0.66, p = 0.015$) in the AHP group. Therefore, the more unaware the AHP patients were (i.e. the higher the Feinberg scores) the greater their impairment in ToM task.

Executive dysfunction and perspective taking

There was a strong correlation in the Go-no-Go subtest of the FAB and 3rd PPT in both the VSPT ($r_s(28) = 0.75, p < 0.001$) and ToM tasks ($r_s(28) = 0.67, p = 0.001$). Therefore,

the worse the patients' performance in the Go-no-Go subtest (i.e. inhibition/set-shifting) of executive functioning the worse their 3rd PPT ability in both experiments.

4.4.2.4 Control tasks

False-belief tasks

In the AHP group, one of the 15 patients failed one false belief question in the age-adapted “Smarties” false-belief task, and four of the 15 patients failed one false belief question in the Sally-Anne task (93% and 87% of questions passed respectively). All healthy controls, and 14 out of 15 HP passed all false belief questions in both experiments (100% and 97% of questions passed, respectively). The difference between the three groups was not significant for the adapted “Smarties” false-belief task ($H(2)=1.12$, $p=0.55$) or Sally-Anne task ($H(2)=3.24$, $p = 0.2$). For both the age-adapted “Smarties” false-belief and Sally-Anne task, all participants passed the reality and memory control questions without exception.

Mental rotation task

A Mann-Whitney-U test was used to compare performance on the mental rotation task between the two patient groups (the task was not administered in the healthy control group). The test revealed that there was no significant difference between groups ($Z = -0.64$, $p = 1$, $r = 0.18$; AHP: median = 50, SD = 10.2; HP: median = 50, SD = 12.9).

4.4.3 Lesion mapping results

Group-level percentage lesion overlay maps for the AHP group ($n = 15$) identified involvement of the fronto-parietal-temporal cortices. Commonly damaged areas included the inferior and medial frontal gyri, the insula ribbon, the supramarginal gyrus, and the dorsal frontal white matter (Figure 4.5A). The HP group ($n = 14$) in comparison presented with a more focal damage largely involving subcortical regions with extension into surrounding fronto-parietal white matter (Figure 4.5B). Lesion volume (in cubic centimetres) was comparable between the AHP (mean = 8.49, SD = 8.00) and the HP group (mean = 5.28, SD = 7.29; $t(27) = -1.13$, $p = 0.27$). Subtraction maps identified clusters around the insula ribbon, inferior and middle frontal gyri (IFG and MFG, respectively), superior temporal gyrus (STG), supramarginal gyrus (SMG), and the pre- and postcentral gyri to differ between the patients groups (Figure 4.6C).

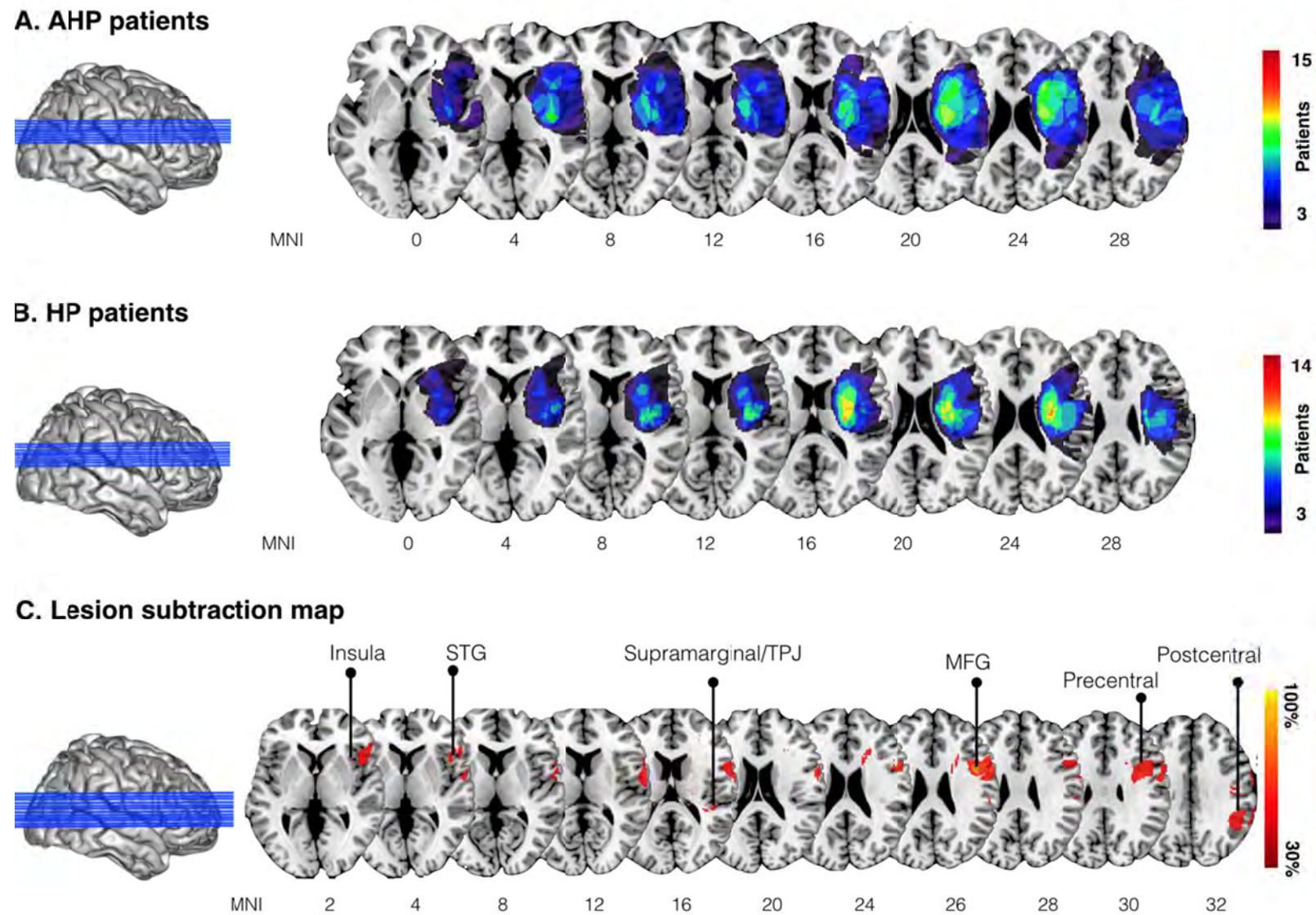
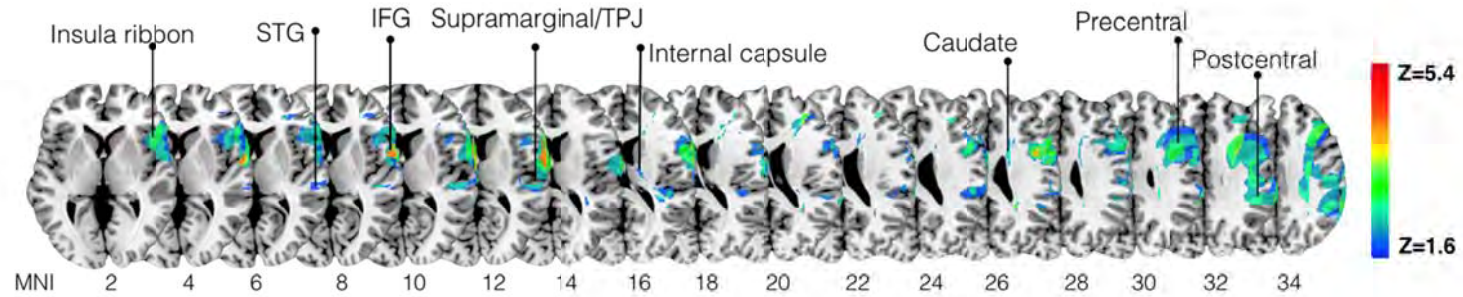


Figure 4.5 Group-level lesion overlay maps for patients with anosognosia for hemiplegia (AHP) and hemiplegic controls

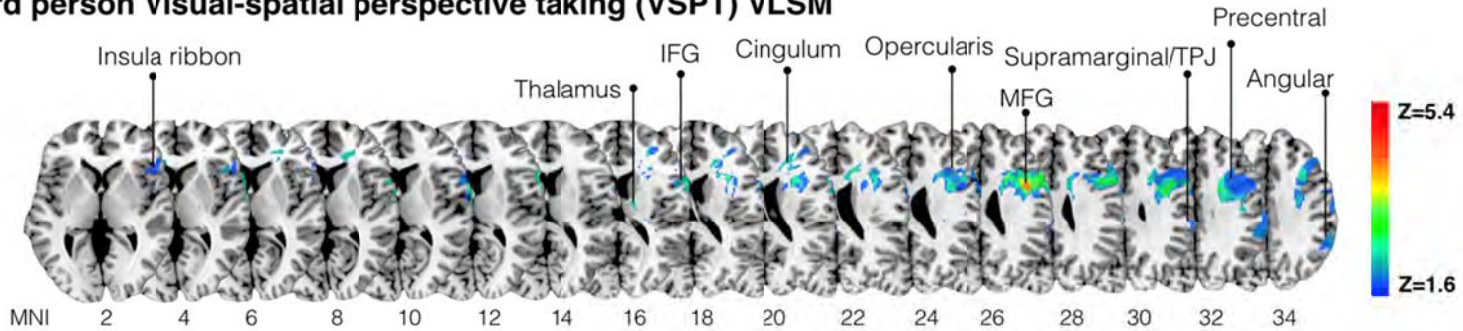
Note: Overlay of lesions in: **A.** patients with anosognosia for hemiplegia (AHP; $n = 15$); **B.** patients without anosognosia (HP; $n = 14$); **C.** statistical analysis comparing the two populations of patients (AHP vs. HP; results are corrected for multiple comparisons, $P < 0.05$ for $Z > 2.1$). IFG = inferior frontal gyrus; MFG = middle frontal gyrus; STG = superior temporal gyrus.

VLSM analysis using the continuous Feinberg awareness scores revealed that voxels within the insula ribbon, supramarginal gyrus (SMG) and STG, as well as the anterior arm of the internal capsule, were significantly associated with motor unawareness (Figure 4.6A). VLSM analysis looking at deficits in 3rd PPT conditions (combining animate and inanimate conditions) in the VSPT experiment identified significant voxels ($p < 0.05$) within the IFG and MFG, SMG, precentral and postcentral gyrus as well as the head of the caudate nucleus and dorsal frontal white matter (Figure 4.6B). The cluster with the maximum Z ($Z = 5.6$) corresponds to the inferior frontal gyrus. The VLSM analysis for the continuous measure of ToM 3rd PPT ability returned significant voxels ($p < 0.05$) in the fronto-parietal cortices, including the IFG, precentral and postcentral gyus, and the supramarginal gyrus. Further, the STG and the dorsal frontal white matter were significantly associated with deficits in 3rd PPT in the ToM (Figure 4.6C). Also for ToM the IFG was the cluster with the maximum Z score ($Z = 5$).

A. Feinberg Awareness Score VLSM



B. 3rd person Visual-spatial perspective taking (VSPT) VLSM



C. 3rd person Theory of Mind (ToM) VLSM

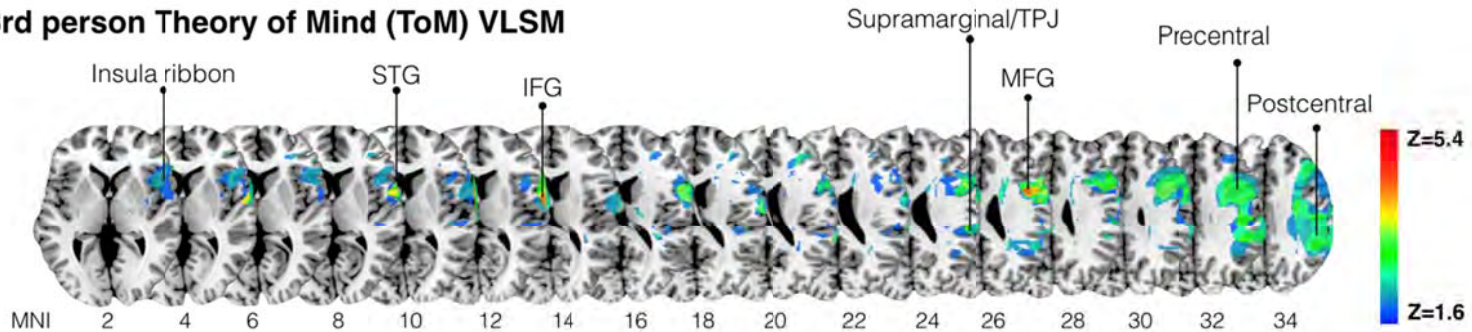


Figure 4.6 Voxel-based lesion-symptom (VLSM) analysis for Feinberg scale and 3rd person perspective taking for VSPT and ToM tasks.

Note: **A.** Damaged MNI voxels predicting the severity of unawareness of symptom deficits (Feinberg scale, inverted, continuous measure) corrected for lesion size and significant at the 5% level after 1000 permutations. **B.** Damaged MNI voxels predicting deficits in 3rd person perspective-taking (animate and inanimate) condition(s) for VSPT task, corrected for lesion size and significant at the 5% level after 1000 permutations. **C.** Damaged MNI voxels predicting deficits in 3rd person perspective-taking ToM task, corrected for lesion size and significant at the 5% level after 1000 permutations.

4.5 Discussion

To the investigators knowledge this is the first experimental study to investigate the relationship between bodily self-awareness and social cognition. The present study used a visual-spatial task and ToM stories to study perspective taking and mentalisation in AHP patients compared to neurological and healthy controls. The main behavioural finding was that AHP patients presented with selective deficits in 3rd PPT compared to 1st PPT relative to both HP control patients and healthy volunteers. Additionally, it appears the more severe their unawareness the greater the deficit in perspective taking. Importantly, there was a strong correlation between 3rd PPT and executive function, specifically set-shifting abilities. The main finding of the lesion analysis, combining experimental and lesion data, showed that 3rd PPT in both visual-spatial and mental perspective taking were associated with lesions to the IFG, MFG, SMG, pre-and-post central gyrus as well as dorsal frontal white matter.

This study also confirms the importance of the right-hemisphere for ToM processes. As predicted, all neurological patients compared to age-matched healthy controls showed selective deficits in social cognitive abilities, in both VSPT and ToM tasks, providing converging evidence of the right-hemisphere's involvement in social cognition (see Happé et al., 1999). Crucially however, AHP patients presented with more severe and specific deficits in mentalising. In the visual-spatial tasks AHP patients had intact self - 1st PPT. However, the capacity to take on other - 3rd person perspectives was markedly impaired in unaware patients. Similarly, AHP patients presented with significantly more impaired ability on 3rd person ToM stories, compared to 1st person stories.

However, the ability to correctly attribute false beliefs was intact in all participants, suggesting that AHP patients are aware of 'other' minds and that basic ToM abilities are intact. The correlation between inhibition control and deficits in 3rd PPT is suggestive of a possible impairment of switching or inhibiting between 1st and 3rd person perspectives. More specifically, apparent deficits in 3rd PPT may not be attributed to 'mind blindness', as these patients are aware of 'other minds' and perspectives, but it is rather indicative of a difficulty to inhibit the 1st person perspective. Other lesion studies have also found unilateral right hemisphere damage to be associated with executive functioning, and more specifically set-shifting or inhibitory control (Griffin et al., 2006; Samson et al., 2005). It has also been proposed that mentalising deficits in Asperger's Syndrome can be

understood as an inability to switch between egocentric and allocentric perspectives, due to several cognitive deficits and/or an impairment in a control mechanisms, resulting in a tendency to be developmentally stuck in an egocentric reality (Frith & de Vignemont, 2005). Social cognitive difficulties in AHP may be similar to those in Asperger's in that they are deficits to cognitive mechanisms that control switching between perspectives. As suggested in Asperger's Syndrome, and possibly AHP, the social world becomes self-centered, egocentrically driven, since they are unable to spontaneously switch or disengage between 1st person (egocentric) and 3rd person (allocentric) viewpoints. Therefore the allocentric, 3rd person, perspective may not exist by itself, but only in relation to the 1st person perspective (also see Turnbull et al., 2014). These egocentric or narcissistic tendencies of AHP patients have been also observed in clinical case studies (Kaplan-Solms & Solms, 2002).

Results of the VLSM using 3rd person perspective taking scores also highlight anatomical areas that have been previously identified as part of a 'mentalising network' (Koster-Hale & Saxe, 2013), specifically the supramarginal (TPJ) and pre-and postcentral gyrus. These results also highlight right frontal-parietal damage to be associated with AHP, which has also been implicated in distinguishing between 1st person and 3rd person mental states (Abu-Akel & Shamay-Tsoory, 2011). The IFG and MFG showed the highest associations with deficits in 3rd PPT in both tasks. Previous studies have shown that the right inferior parietal cortex, precuneus and somatosensory cortex are specifically involved in distinguishing self and other mental states (Ruby & Decety, 2001). Additionally, the IFG (Uddin et al., 2007; Uddin et al., 2005) has been implicated in facilitating this distinction through attentional systems. Abu-Akel & Shamay-Tsoory (2011) propose that both the ventral and dorsal attentional systems act together through the MFG, linking attentional and mentalising functions to process 1st person and 3rd person mental states. Furthermore, recent studies have suggested that the right IFG plays a particular role in set-shifting and inhibition, which is required for the suppression of responses (Samson et al., 2005). Therefore, this proposed impairment in spontaneously switching or disengaging between 1st and 3rd person perspectives might be a consequence of damage to the IFG and MFG specifically.

Fluctuations in awareness have also been reported following questions in the 3rd person rather than 1st person perspective (i.e. "In your present state how well can you move your left arm?" vs. "If I were in your present state...?"; Marcel et al., 2004). Recent

experimental case studies have also shown that video replay, which provides 3rd person and offline (at a time different than the one in which the patient initiated the movement) visual feedback, either immediately or gradually restores motor awareness in some AHP patients (Fotopoulou et al., 2009; see Chapter 6). In comparison, results from our study suggest that AHP patients do not spontaneously see themselves from a 3rd person perspective. Therefore viewing themselves from a 3rd person perspective in mirrors, video playback or discussions in the 3rd person may help facilitate an integration of these perspectives. This may therefore result in an increase or reinstatement of motor awareness either immediately or overtime, depending on the severity of deficits in perspective taking or the size and location of the lesion.

In regards to the general anatomical substrates of AHP, the results confirmed a combination of involvement of both cortical and subcortical areas, as well as dorsal frontal white matter. Previous studies identifying the neuroanatomical substrates of AHP have mostly drawn on non-statistical lesion overlay methods or binomial tests (Berti et al., 2005; Karnath et al., 2005). In contrast to such lesion subtraction studies, a voxel-base lesion-symptom mapping approach (Bates et al., 2003; Rorden et al., 2007; Vocat et al., 2010) was used. In the current study, the presence (lesion overlay and subtraction) and severity of AHP, using Feinberg VLSM results, highlight lesions to the IFG and MFG (premotor areas), as previously identified by Berti et al. (2005) and Korte et al. (2014), as well as the insula ribbon as first shown by Karnath et al. (2005). The STG and SMG, the caudate nucleus, as well as dorsal frontal white matter were further anatomical correlates highlighted by these lesion mapping results, which have been confirmed by previous studies (Fotopoulou et al., 2010; Moro et al., 2011).

4.5.1 Limitations

However, it is important to recognise that interpretation of the neuroanatomical correlates identified are limited by the small sample size and inherit limitations to the lesion mapping approach (Geva et al., 2012; Rorden et al., 2007; Volle et al., 2012). Nevertheless, all previous lesion mapping studies in AHP are subject to similar limitations, with this study being one of the few that has directly compared experimental scores with lesion data. Future studies will have to use better structural lesion data and fMRI paradigms to be able to more accurately identify brain areas related to AHP and its association with experimental measures. Although all experiments have been based on previously validated tasks and extensively piloted, these experimental results are limited

by the use of non-validated measures. However, in working with acute brain damaged patients all experimental measures must be adapted to be used at the bedside with acute and elderly stroke patients. Furthermore, to the investigators knowledge this is one of the first studies to investigate both the mental states/perspectives of others using ToM stories, and visual spatial perspective taking, which elucidates the embodied nature of perspective taking. This embodied view of self-representation remains a relatively unexplored area in AHP and holds the promise of significantly enhancing our understanding of the dynamic interaction between the social and embodied view of the self. Lastly, the current study has shown that AHP patients present with specific deficits in mentalising abilities; however, future studies should investigate mentalisation and difference in perspective taking in direct relation to disability related or anosognosic specific material.

Chapter 5 Partiality of motor awareness: self and other referent processes in anosognosia for hemiplegia

5.1 Introduction

As previously discussed in Chapter 1, the clinical presentation of anosognosia for hemiplegia (AHP) can vary considerably (Fotopoulou, 2012). Clinical characteristics, such as the *degree*, *extension*, *partiality* (i.e. if patients have partial knowledge or awareness of their motor weakness depending on the question asked or social context) and *specificity* of unawareness can differ noticeably between patients (see Chapter 1). In regards to *partiality* of motor unawareness, a conflicting clinical observation has been frequently observed in that unaware patients deny their motor weakness, but are still willing to stay in the hospital, participate in treatment, and/or use a wheelchair (Prigatano & Weinstein, 1996; Bisiach & Berti, 1995; also see Mograbi & Morris, 2013). These observations suggest that AHP patients may have some partial knowledge of their motor impairments. In a single case study House and Hodge (1988) demonstrated this partiality of awareness by showing an anosognosic patient photographs of patients with and without motor disabilities. The patient was able to correctly identify that specific patients had motor impairments in the photographs. Interestingly, when asked to identify the person in the photograph “most like her”, she choose a picture of a patient in a wheelchair as the most similar to herself. These results again demonstrate that, depending on the condition, some anosognosic patients may to have partial knowledge of their motor deficits.

Marcel et al. (2004) and colleagues followed up on these clinical observations and conducted the first systematic study on partial knowledge of hemiplegia. The experimental task identified differences in how patients reported unawareness depending on if questions were directed to the patient’s own motor deficits or that of another paralysed person. Patients were asked to rate their own or the ‘other’ persons’ motor ability on bimanual and bipedal actions using an 11-point scale. The more patients overestimated their motor ability on the tasks the greater their unawareness of motor paralysis. Between 15% and 50% of AHP patients with right-hemisphere damage showed greater unawareness ‘in the self’ condition than the other. Therefore, AHP patients tended to overestimate their own motor ability (i.e. more unaware in the self condition) compared to the ability of another hemiplegic patient.

There is however some confusion in the literature as to what is defined as 1st and 3rd person perspective, compared to self referent and other referent differences. For example, in the original Marcel et al. (2004) paper, 1st person was equated to the self referent and similarly 3rd person was paralleled to other referent. There can be conceptual differences in visual perspective taking (e.g. using videos and mirrors) and verbal perspective taking (e.g. ToM stories, see Chapter 4). For the purpose of this chapter however, 1st versus 3rd person perspective taking is conceptually different from self referent versus other referent differentiation. This study will investigate the partiality of motor awareness using verbal 1st person and 3rd person perspective taking, as well as testing if there is partial knowledge or differences between self referent versus other referent conditions on unawareness. Taken together, it is therefore important to recognise that what is defined here as a 3rd person perspective is conceptually different to that of Marcel et al. (2004), as well as House & Hodge (1988).

In a case-series investigation with three AHP patients, Ramachandran & Rogers-Ramachandran (1996) explored whether motor unawareness of one's own paralysis generalises to include the disabilities of other people. Two of the patients denied the disability of a 'stooge' hemiplegic patient who was seated in a wheelchair next to them. The authors concluded that at least some anosognosic patients deny the paralysis of another patient. Moro and colleagues (2011) further investigated this hypothesis using self referent and other referent awareness interviews. Eleven AHP patients were asked to rate their own motor abilities on a set of complex actions (e.g. getting dressed, driving a car etc.). They were asked the same questions referring to the motor ability of an age and gender matched hemiplegic patient, who was seated in a wheelchair in front of them. Four patients were unaware only in the self referent interview and seven were unaware in both the self-and-other referent interviews. Using clinical CT scans and lesion mapping methods, Moro and colleagues identified anatomical areas associated with scores in the self-and-other awareness interview. Regions associated with the self and other condition included the central sulcus, the frontal inferior and superior area and supplementary motor area. The ability to distinguish between the self versus the other has similarly been associated with right frontal and motor areas, including the inferior and middle frontal gyrus (IFG and MFG; Abu-Akel & Shamay-Tsoory, 2011). Superior-temporal areas (e.g. superior temporal gyrus, STG and temporal parietal junction, TPG) have likewise been commonly associated with mentalising or ToM abilities (Koster-Hale & Sax, 2013; see Chapter 4 for details).

As previously discussed in Chapter 1 and Chapter 4, presenting visual 3rd person feedback using videos and mirrors can lead to either temporary or permanent remission of AHP, as well as disorders of body ownership (e.g. somatoparaphrenia; Fotopoulou et al., 2009; Fotopoulou et al., 2011; Jenkinson et al., 2013; also see Chapter 6). Additionally, in the previous chapter it was shown that AHP patients have a specific deficit in 3rd person perspective (PP) taking in a visual-spatial task and ToM stories. However, no study has investigated these deficits in perspective taking in relation to disability related items.

The aim of the current study was to investigate the partiality of motor unawareness in two ways, through investigating differences in: (1) 1st person versus 3rd person perspective (PP); and (2) self referent versus other referent conditions. Accordingly, three experiments were conducted to explore perspective taking and self-other reference in motor awareness tasks. Experiment 1 was designed to investigate whether there are differences in motor unawareness when asked from a 1st PP versus a 3rd PP in a self referent condition. The purpose of Experiment 2 was to specifically test if AHP patients were aware of the paralysis of another paralysed patient shown in a video, and if there are differences in 1st PP and 3rd PP in an other referent condition. The aim of Experiment 3 was to directly compare the difference between self referential and other referential processes in motor unawareness using disability related ToM stories. Furthermore, since Experiment 3 allowed for a direct comparison between self and other referent differences in motor awareness, the experimental results of the difference between self and other awareness was used in a voxel-based lesion-symptom (VLSM) analysis (see Chapter 2 for methods). This allowed for the comparison between the associated brain areas with anosognosia, and the difference in self and other referent awareness questions. It was predicted that AHP patients would overestimate their abilities when asked from a 1st person perspective, but have more accurate estimates when asked from a 3rd person perspective. Furthermore, it was expected that most patients' anosognosia would extend to include the paralysis of another hemiplegic patient (i.e. be unaware of the motor deficits of another paralysed patient). Finally, a difference in the severity of unawareness was predicted, with AHP patients being more aware (i.e. less anosognosic) of the disabilities of the other patients compared to their own paralysis.

5.2 General methods and results

5.5.1 Patients

Thirty-eight right-handed, adult neurological patients with right-hemisphere lesions participated in the studies below (19 females, mean age = 65.97, SD = 16.13 years; age range: 33-97). Patients were recruited from consecutive admission to three acute stroke wards and one rehabilitation clinic using the standard inclusion and exclusion criteria described in Chapter 2.

Patients were divided into two groups based on their classification of anosognosia using the Berti et al. (2005) and Feinberg et al. (2000) measures as specified in Chapter 2. Nineteen patients were classified as having AHP (11 females; mean age = 67.68, SD = 16.32 years; age range: 33-86) and 19 patients were classified as hemiplegic (HP) controls (8 females; mean age = 64.26, SD = 15.95 years; age range: 41-87).

5.5.2 Statistical analysis

All behavioural analyses were conducted in SPSS (IBM Corp, 2013). For analysis of neurological and neuropsychological tests, non-parametric Mann-Whitney *U* tests were used (owing to the non-normal data distribution) to analyse the difference between the two patient groups. For these analyses only, the alpha significance level was set to $\alpha < 0.01$ to account for multiple comparisons. Analyses of all experimental investigations below were also conducted using non-parametric tests (owing to the non-normal data distribution), applying a Bonferroni correction where appropriate.

5.5.3 Neurological and neuropsychological testing

In addition to the above anosognosia assessments, the neurological and neuropsychological profile of the patients was formally assessed using measures described in Chapter 2. A summary of the neuropsychological and neurological profile of the patients is provided in Table 5.1. No significant difference was observed for age, years of education, pre-morbid IQ, long-term memory recall and general cognitive functioning between groups (all p 's > 0.12). The groups did not differ in their time of symptom onset and assessment interval, orientation or working memory (all p 's > 0.37). As expected there was a significant difference in awareness between the AHP and HP patients (Berti interview: $Z = -5.55$, $p < 0.001$, $r = 0.9$; Feinberg scale: $Z = -5.19$, $p < 0.001$, $r = 0.84$). Both groups were also within the normal range for the general Hospital Anxiety and Depression Scale. AHP patients performed significantly worse on tests of

proprioception compared with HP patients ($Z = -3.17$, $p < 0.001$, $r = 0.51$). Both patient groups presented with similar visual and sensory deficits, as well as visual-spatial and personal neglect (see Table 5.1). Although not significantly different, neglect was marginally greater in the AHP group (e.g., star cancellation: $Z = -2.04$, $p = 0.04$, $r = 0.33$; Comb/Razor test of personal neglect percentage bias: $Z = -2.72$, $p = 0.01$, $r = 0.44$). Both patient groups performed outside the normal range on the Cognitive Estimates Test, suggesting possible deficits in abstract reasoning, however, there was no statistical difference between groups (AHP vs. HP; $Z = -0.52$, $p = 0.62$). There was a trend towards significance between patient groups for the overall FAB score ($Z = -3.05$, $p = 0.01$, $r = 0.49$) and a significant difference between groups on the go-no-go subtest ($Z = -3.33$, $p < 0.001$, $r = 0.54$).

Table 5.1 *Groups' demographics and neuropsychological profile*

| | AHP | | HP | | Mann-whitney | |
|-------------------------------|-----------------|----------------|----------------|------|---------------------|-------|
| | Median | IQR | Median | IQR | Z | p |
| N | 19.00 | - | 19.00 | - | - | - |
| Age (years) | 73 | 22 | 62 | 26 | -0.64 | 0.53 |
| Education (years) | 11.50 | 4.25 | 12.00 | 4.75 | -0.98 | 0.34 |
| Days from onset | 9.00 | 11 | 10.00 | 19 | -0.23 | 0.82 |
| MRC Left upper limb | 0.00 | 0 | 0.00 | 0 | -0.57 | 0.53 |
| MRC left lower limb | 0.00 | 1 | 1.00 | 2 | -0.65 | 0.53 |
| Premorbid IQ-WTAR | 40.00 | 17.5 | 36.00 | 13.3 | -0.38 | 0.73 |
| Berti awareness interview | 2 ^a | 1 | 0.00 | 0 | -5.55 | 0.00* |
| Feinberg awareness scale | 6 ^a | 3.25 | 0.00 | 0.5 | -5.19 | 0.00* |
| Orientation | 3.00 | 0 | 3.00 | 0 | -0.52 | 0.67 |
| Digit span forwards | 6.00 | 1.25 | 6.00 | 3.25 | -0.11 | 0.92 |
| Digit span backwards | 3.00 | 2 | 4.00 | 2 | -0.93 | 0.37 |
| MOCA memory | 4.00 | 2 | 5.00 | 1.5 | -1.53 | 0.12 |
| MOCA | 24.23 | 7.75 | 25.50 | 6.63 | -0.33 | 0.77 |
| Visual fields | 4 ^a | 2 | 4 ^a | 6 | -0.32 | 0.76 |
| Somatosensory (max 6) | 3 ^a | 2 | 2 ^a | 4.5 | -0.73 | 0.48 |
| Proprioception (max 9) | 4.50 | 4.25 | 8.00 | 2 | -3.71 | 0.00* |
| Comb/razor test bias | -0.43 | 0.27 | -0.08 | 0.43 | -2.72 | 0.01 |
| Comb/razor test left | 3.00 | 3.50 | 5.00 | 5 | -2.86 | 0.00 |
| Comb/razor test right | 10.00 | 5.50 | 9.00 | 4 | -0.53 | 0.61 |
| Comb/razor test ambiguous | 5.00 | 4.00 | 6.00 | 3 | -0.04 | 0.98 |
| Bisiach one item test (max 3) | 1.00 | 1.50 | 1.00 | 1 | -0.69 | 0.50 |
| Star cancelation (omissions) | 40 ^a | 20.5 | 14.25 | 33.3 | -2.04 | 0.04 |
| Line bisection | 0 ^a | 2 | 2.00 | 2 | -2.61 | 0.01 |
| Copy | 0 ^a | 1 ^a | 1.00 | 1.5 | -2.04 | 0.05 |
| Representational drawing | 0.00 | 0 | 1.00 | 1 | -2.79 | 0.01 |
| Cognitive estimates | 9 ^a | 7.5 | 9 ^a | 9.5 | -0.52 | 0.62 |
| FAB total score | 10.00 | 3.5 | 14.00 | 5.5 | -2.56 | 0.01 |
| Similarities | 2.00 | 1.25 | 2.00 | 1 | -1.44 | 0.18 |
| LexialFluency | 2.50 | 1 | 2.00 | 1.75 | -1.97 | 0.05 |
| MotorSeries | 2.00 | 1 | 2.00 | 2.75 | -0.80 | 0.43 |
| ConflictIns | 3.00 | 1.25 | 2.00 | 2 | -1.96 | 0.05 |
| GonoGo | 0.50 | 1 | 3.00 | 1.75 | -3.33 | 0.00 |
| PresBehav | 3.00 | 1 | 2.00 | 0 | -1.63 | 0.10 |
| HADS depression | 6.00 | 6 | 7.00 | 6.38 | -1.62 | 0.11 |
| HADS anxiety | 8.00 | 7 | 6.50 | 10.8 | -0.39 | 0.72 |

Medical Research Council (Guarantors of Brain, 1986); MOCA=The Montreal Cognitive Assessment (Nasreddine, 2005); Comb/razor test = tests of personal neglect (McIntoch et al., 2000); Bisiach one item test= test of personal neglect; Visual fields and somatosensory= customary 'confrontation' technique= Bisiach et al. (1986); line crossing, star cancellation, copy & representational drawing= conventional subtests of Behavioural Inattention Test (Wilson et al., 1987); FAB= Frontal Assessment Battery (Dubois et al., 2000); HADS=Hospital Anxiety and Depression scale (Zigmond, & Snaith,1983).

^a Scores below tests' cut-off points, or more than 1 SD below average mean.

*Significant difference between groups, $p < 0.05$

5.3 Experiment 1: Self awareness

5.5.1 Patients and design

Of the 38 patients, five were excluded from this experiment due to time constraints (e.g. unavailability due to other clinical sessions and patient transfer); therefore 34 patients participated in the current study. Seventeen patients were classified as having AHP (10 females, mean age = 67.65, SD = 16.89 years) and 17 as HP controls (8 females, mean age = 63.29, SD = 15.11 years) using the assessment criteria specified above (also see Chapter 2).

The main experimental design included one between subject factor (Group: AHP vs. HP patients), and one within subject factor (Self Verbal Perspective Taking: 1st person vs. 3rd person). This allowed for a 2 x 2 experimental design on the main dependent variable: awareness ratings (see Section 5.5.2 below for details). Awareness ratings were calculated using a composite score, comprising of general awareness ratings and awareness for actions (5 bimanual actions and 2 bipedal actions based on Marcel et al., 2004) from a questionnaire (see below for details).

5.5.2 Materials

The experimental task was based on Marcel et al.'s (2004) estimates of current ability task. An awareness questionnaire was designed, based on validated measures (Bisiach et al., 1986; Marcel et al., 2004), consisting of 10 questions. The questionnaire was divided into two sections: (1) general awareness questions; and (2) awareness of ability to perform bimanual and unimanual actions. Three general awareness questions were first asked: "Is there anything wrong with your movement since the stroke?"; "Can you move your left arm as normal?"; and "Can you move your left leg as normal?". In the second part, patients were asked to rate their motor ability on seven actions used by Marcel et al. (2004). The actions consisted of five bimanual and two bipedal actions, specifically: tie a knot; clap hands; shuffle cards; row a boat; unscrew a bottle; climb a ladder; and jump. Two sets of the questionnaire were developed. Set one asked patients to judge their motor abilities from their own perspective- 1st person perspective (e.g. "Can you move your left arm as normal?"). Set two asked patients to judge their motor abilities from the perspective of the physiotherapist- 3rd person perspective (e.g. "If the physiotherapist were here now, would he/she think you could move your left arm as normal?").

5.5.3 Procedures and scoring

The questions were all read out-loud to the patients, in a slow pace and neutral tone. Questions were repeated on request of the patient or if the examiner felt it was necessary due to distraction or fatigue reasons. The order of the presentation of the two sets (1st PP and 3rd PP) was counterbalanced and there was a five-minute break between the administration of both sets. On presentation of the 1st PP set, patients were asked to answer questions and judge their motor ability from their *own* perspective. On presentation of the 3rd PP set, patients were instructed to judge their own motor ability from the perspective of the physiotherapist (e.g. “If the physiotherapist was here now, would he/she think that you can...”).

Patients were first asked to make a spontaneous response for the three general awareness questions, which the examiner wrote down in full. Patient were then asked to rate their ability on each of the seven action items using an 11-point Likert-type scale: “*From your perspective, in your present state, how well compared with your normal ability, from a scale from 10 – you can do it as well as usual- to 0 –you cannot do it at all- can you...(e.g. tie a knot)*”; or “*From the physiotherapists perspective, in your present state, how well compared with your normal ability, from a scale from 10 – you can do it as well as usual- to 0 –you cannot do it at all- does the physiotherapist think you can...(e.g. tie a knot)*”. The 11-point rating scale was read out-load to the patients and also presented visually as a vertical scale on an A4 sheet of paper (0 at the bottom and 10 at the top), positioned in the patient’s right visual field in order to minimise possible unilateral visual neglect effects. Patients were familiarised with the rating scale before the experiment began.

The three general awareness questions were scored using a modified version of the Feinberg scoring method: 0 = no unawareness of deficit; 5 = partial unawareness of deficit; and 10 = complete unawareness of deficit (maximum score = 30; the higher scores indicate greater unawareness). The seven motor-related actions were scored using the ratings given by the patients from 0-10 (0 = cannot perform the action at all; 10 = can perform the action as well as usual). Therefore generating a total maximum score of 70 for action related items (higher scores indicate greater unawareness). The general and motor ability questions were combined to generate a total score of 100.

5.5.4 Results

Main effects

A Mann-Whitney U test confirmed that there was a significant main effect of Group ($Z = -4.30$, $p < 0.001$, $r = 0.74$), with the AHP group (median = 53) being significantly less aware than the HP group (median = 7.5). A Wilcoxon signed rank test on the main effect of Self Verbal PT on the self revealed that patients were significantly more aware overall in the 3rd person Verbal PT condition (median = 20) than the 1st person Verbal PT condition (median = 29; $Z = -2.07$, $p = 0.038$, $r = 0.36$).

Interaction effects

The interaction between Group and Verbal PT was analysed by calculating the difference between 1st person and 3rd person in the Verbal PT conditions, and analysing the effect of Group on this difference. A Mann-Whitney U test revealed a significant interaction ($Z = -3.59$, $p < 0.001$, $r = 0.62$). Bonferroni corrected post hoc analysis ($\alpha = 0.025$) showed that in the AHP group patients were significantly more aware in the 3rd person Verbal PT condition (median = 46) than the 1st person Verbal PT condition (median = 59; $Z = -2.79$, $p = 0.003$, $r = 0.48$) for the self (see Figure 5.1). By contrast, in the HP group there was no significant difference between the 3rd person Verbal PT condition (median = 5) and 1st person Verbal PT condition (median = 8; $Z = -1.07$, $p = 0.308$, $r = 0.12$).

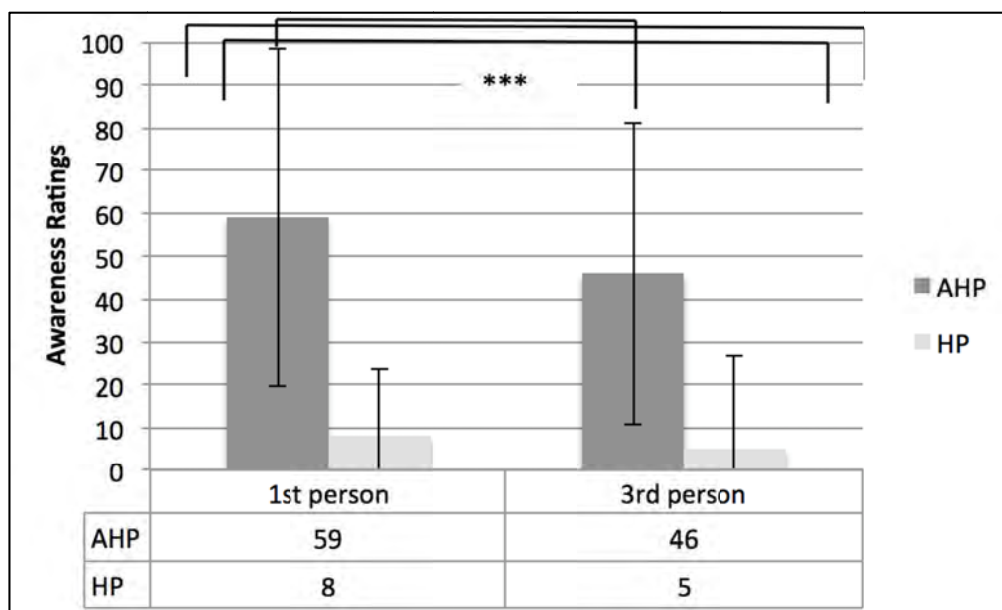


Figure 5.1 Awareness ratings for 1st and 3rd person verbal perspective taking referring to the patient (self awareness).

Note: Medians and interquartile range.

5.4 Experiment 2: Other awareness

5.5.1 Patients and design

As in the experiment above, of the 38 patients, five were excluded due to time constraints (e.g. unavailability due to other clinical sessions and patient transfer); therefore 34 patients participated in the current study. Seventeen patients were classified as having AHP (10 females, mean age = 67.65, SD = 16.89) and 17 as HP controls (8 females, mean age = 63.29, SD = 15.11) using the assessment criteria specified above.

The main experimental design included one between subject factor, Group (AHP vs. HP patients) and one within subject factor (Other Verbal Perspective Taking: 1st person vs. 3rd person). This allowed for a 2 x 2 experimental design on the main dependent variable: awareness ratings. The awareness rating was calculated using the same composite score from the questionnaire as in Experiment 1.

5.5.2 Materials

A 40 second video clip of an ‘other’ paralysed person was filmed using a portable digital video camera (Sony Hanycam, DCR-SR57). Two videos were filmed of a female and male ‘stooge patient’, and shown to the patients according to gender. The video of the male and female ‘stooge’ patient was identical in regards to: the examiner assessing the patient; the room and wheelchair used; and the questions asked in the video. In each video the patient was sitting in a wheelchair, with the left-side of their body visually paralysed (i.e. the patient is in a wheelchair, and their left arm and leg are limp in the video). The patient’s face was not visible in the video, but the full body (both right and left upper and lower limbs) was visible. The examiner is kneeling beside the patient with full body and face visible. In the video, the examiner asks the ‘stooge’ patient to move his/her right arm and leg, which the patient is able to do. The examiner then asks the patient in the video to move his/her left arm and leg, which the patient was unable to perform. The patient first fails to move his/her left arm and then left leg. In the video, the examiner asks a series of questions that requires the patient to perform specific movements (e.g. “Please try and move your left arm for me now?” or “Good, but try and move your left arm, without the help of your right arm.”). The patient in the video does not offer any verbal reply, and only moves or attempts to move his/her arm and leg. The examiners questions (i.e. asking the patient to perform specific movements as explained above) are fully audible in the video.

The same awareness questionnaire described in Experiment 1 was used to rate how aware AHP patients were of the motor disabilities of the ‘stooge’ patient in the video. Questions consisted of general awareness questions and ratings of seven action-related items. Both the 1st PP and 3rd PP set were used as described in Experiment 1.

5.5.3 Procedure

Firstly, a laptop computer (screen size 13) was placed on a hospital table directly in front of the patient, 50 cm from him/her and, to exclude possible effects of neglect deficits, 20 cm right from the centre of his/her visual fields. Patients then proceeded to watch the 40-second video clip described above with sound.

Immediately after the video-viewing the same questionnaire, as described in Experiment 1, was administered. However, patients were asked to judge the motor ability of the other paralysed patient they saw in the *video*. The questions were all read out-loud to the patients, in a slow pace and neutral tone. The order of the presentation of the two sets (1st PP and 3rd PP) was counterbalanced and there was a five-minute break between the administration of both sets. On presentation of the 1st PP set, patients were asked to answer questions judging the motor ability of the other hemiplegic patient in the *video* from their own perspective (e.g. “Can the patient in the video move their left arm as normal?” or “Referring to the patient in the video, how well can he/she tie a knot?”). On presentation of the 3rd PP set, patients were instructed to judge the motor ability of the other hemiplegic patient in the *video* from the perspective of the physiotherapist (e.g. “Would the physiotherapist think the patient in the video can move their left arm as normal?” or “If the physiotherapist was here now, would he/she think the patient in the video could tie a knot...”). The questionnaire was scored using the same scoring method described in Experiment 1.

5.5.4 Results

Main effects

A Mann-Whitney U test confirmed that there was a significant main effect of Group ($Z = -2.53$, $p = 0.01$, $r = 0.43$), with the AHP group (median = 24) being significantly more unaware regarding the abilities of the ‘other’ hemiplegic patient compared with the HP group (median = 7.5; see Figure 5.2). A Wilcoxon signed rank test on the main effect of Verbal PT revealed no overall significant difference between 3rd person Verbal PT condition (median = 17) and the 1st person Verbal PT condition (median = 18; $Z = -0.40$,

$p = 0.703$, $r = 0.069$).

Interaction effects

The interaction between Group and Verbal PT was likewise analysed by calculating the difference between 1st person and 3rd person Verbal PT conditions on the other hemiplegic patient, and analysing the effect on Group. This interaction was not significant ($Z = -0.86$, $p = 0.404$, $r = 0.15$).

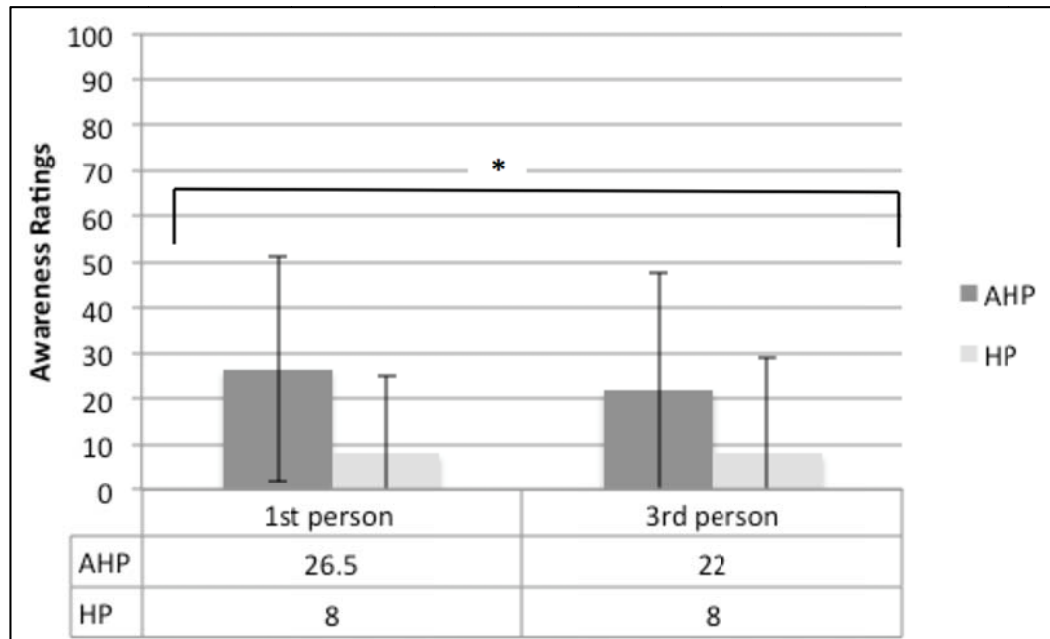


Figure 5.2 Awareness ratings for 1st and 3rd person verbal perspective taking for the other (video) hemiplegic patient.

Note: Medians and interquartile range used.

5.5 Experiment 3: Disability related ToM stories

5.5.1 Patients and design

Disability related ToM stories were based on those explained in Chapter 4. Stories were adapted based on previous story-based tests (Hynes et al., 2006), which required participants to understand the mental states (e.g., beliefs, intentions or emotions) of different people in the stories. All thirty-eight patients participated in this study. The main experimental design included one between subject factor, Group (AHP and HP patients) and two within subject factors, Reference (self referent and other referent) and Order (1st order and 2nd order). This design allowed for a 2 x 2 x 2 design on the main dependent variable of percent of correct response on ToM stories. Accordingly, the better the

patients performance on the disability related ToM stories, the more aware they were of motor deficits of the character in the story.

5.5.2 Materials

Disability related ToM stories were designed by adapting classical ToM stories used by Hynes et al. (2005). Sixteen stories were created: 12 target stories and 4 physical control stories, of carefully matched characteristics. All stories consisted of at least two characters and were followed first by an open ToM question and then by three multiple-choice responses (as in Hynes et al., 2005; Figure 5.3). The content of the 12 disability related ToM stories always consisted of the character having had a stroke and losing left-sided motor functions. Eight of the stories (six ToM and two control) were related to the *self* (e.g. “You have had a stroke...”), while the other eight were related to the *other* (e.g. “Peter has just had a stroke...”; see Appendix N for examples of stories). Half of the ToM stories were followed by a question about the mental state of one of the character (1st Order), while the other half consisted of an extension of the original story and were followed by a 2nd order question. In eight of the disability related ToM stories the character was aware of their disabilities (four in the self referent condition and four in the other referent condition). In the remaining four of the disability related ToM stories the character was unaware of their left-sided paralysis (two in the self referent condition and two in the other referent condition). The physical control stories were similar to the ToM stories and involved social situations, but the questions required inferential reasoning and semantic knowledge rather than perspective taking, and did not have disability related content.

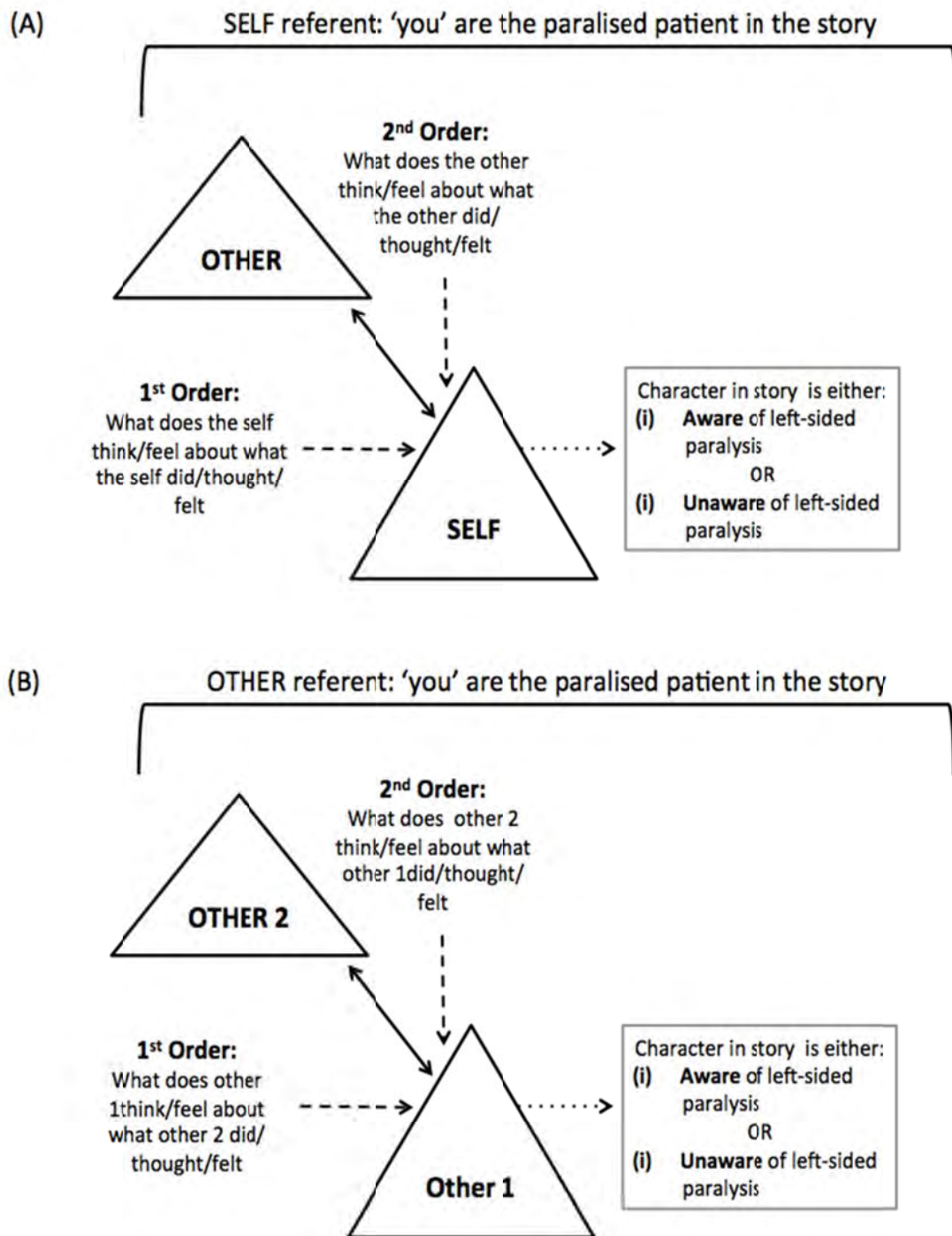


Figure 5.3 Figure representing the self referent and other referent sets of disability related ToM stories

Note: **A.** Self referent ToM stories depicting the 2 actors (self and other) with “you” as the person with the disability in the story. The character in the story is either aware or unaware of their left-sided paralysis. The dotted arrows represent the 1st order and 2nd order levels. **B.** Other referent ToM stories depicting the 2 actors (other 1 and other 2) with the other 1 character having a disability in the story. The character in the story is either aware or unaware of their left-sided paralysis. The dotted arrows represent the 1st order and 2nd order levels.

5.5.3 Procedure and scoring

The administration of the task was identical to that of the ToM stories described in Chapter 4. Accordingly, all stories and questions were read out-loud to the participants. The participants were first required to make a spontaneous response, which the examiner wrote down in full. Subsequently, the experimenter read the multiple-choice options and participants had to indicate their choice verbally, which all patients were able to do. Of the multiple-choice options given, there was only one possible correct answer, the other options being either (i) the incorrect belief or (ii) irrelevant or incoherent with the story. For each question a composite score was calculated using both the multiple-choice answers and the spontaneous answer. Multiple-choice answers were scored as 1 = correct and 0 = incorrect. Spontaneous answers were scored as 1 = correct, 0.5 = partially correct/inadequate and 0 = incorrect. Two raters scored the spontaneous answers independently. Interclass correlation coefficient of 0.92 indicated a good agreement between raters. Divergent scores (<2% of stories) were discussed and jointly agreed on. Total scores were converted into percentages and used in the statistical analyses.

In the patient groups, testing was conducted in two successive sessions to avoid fatigue. The order of the presentation of the two sets (1st PPT and 3rd PPT) was counterbalanced. Each set began and ended with a control story. To check for comprehension, following each control story, all participants were asked to rate how well they understood the story. As in Chapter 4, a 5-point Likert-type scale was used (i.e. *“Using this scale from one to five, how well did you understand the story? One being the lowest score, where you understood very little, and 5 being the highest score, where you understood the whole story”*). The task was piloted on four neurological patients (two AHP and two HP) to test for comprehension of stories and questions, possible attentional biases in the patient group and other testing considerations. The results confirmed the suitability of the stories and questions but minor corrections were made on the readability of the specific stories.

5.5.4 Lesion mapping methods

Routinely acquired clinical scans (CT and/or MRI) were obtained for all 38 patients within the first week of symptom onset. Lesion mapping methods specified in Chapter 2 were followed for analysis below. Separate VLSM analyses were run for the following dependent variables (continuous scores): i) Feinberg awareness scores; and ii) differential scores (other – self) from the disability related ToM stories. For these behavioural measures, a lower score corresponded respectively to lower awareness and poorer

performance on disability related ToM stories. Feinberg awareness scores were not available for four patients (2 AHP and 2 HP), consequently those patients were excluded from the VLSM for Feinberg scores and analysis was run on 34 patients respectively.

5.5.5 Behavioural results

Control condition and comprehension ratings

All participants performed close to the ceiling level for physical control stories with AHP patients passing 84.21% and HP patient passing 89.47% questions, respectively. There was no significant difference between groups ($Z = -1.63$, $p = 0.10$, $r = 0.26$). All participants reported comprehension ratings between four and five.

Main effects

A Mann-Whitney U test confirmed that there was a significant main effect of Group ($Z = -4.80$, $p < 0.001$, $r = 0.78$), with the AHP group (median = 45.83) performing significantly worse in the disability related ToM stories compared to the HP group (median = 78.12; see Figure 5.4). A Wilcoxon signed rank test on the main effect of Reference was not significant, however there was a trend towards significance ($Z = -1.94$, $p = 0.052$, $r = 0.31$). The main effect of Order was significant as shown by a Wilcoxon signed rank test ($Z = -4.54$, $p < 0.001$, $r = 0.74$), with patients doing better in 1st Order questions (median = 75) compared to 2nd order questions (median = 47.92).

Interaction effects

The interaction between Group and Reference was analysed by calculating the difference between self and other referent conditions, and analysing the effect of Group on this difference using a Mann-Whitney U test, revealing a significant interaction ($Z = -3.01$, $p = 0.002$, $r = 0.49$). Bonferroni corrected post hoc analysis ($\alpha = 0.025$) showed that in the AHP group patients performed significantly better in the other referent stories (median = 52.08) compared with the self referent stories (median = 33.33; $Z = -2.85$, $p = 0.003$, $r = 0.46$). By contrast, in the HP group there was no significant difference between the other referent (median = 77) and self referent (median = 77.03; $Z = -0.48$, $p = 0.654$, $r = 0.08$).

The interaction between Reference and Order was likewise analysed by calculating their relevant differential scores and comparing their difference using a Wilcoxon signed rank test revealing a significant interaction ($Z = -2.16$, $p = 0.03$, $r = 0.35$). Post-hoc analysis

with Bonferroni corrections ($\alpha = 0.0125$) showed that in self referent condition there was a significant difference between 1st Order and 2nd Order responses ($Z = -3.61$; $p < 0.001$, $r = 0.59$), with patients doing better in the 1st Order questions (median = 66.67) compared to the 2nd Order questions (median = 50). Similarly, there was a significant difference in the other referent condition between 1st Order and 2nd Order questions ($Z = -4.23$, $p < 0.001$, $r = 0.69$), with patients having higher scores in the 1st Order (median = 83.33) compared to the 2nd Order (median = 50). There was also a significant difference between the Self Referent, 1st Order questions and the Other Referent, 2nd Order questions ($Z = -3.62$, $p < 0.001$, $r = 0.59$), with patients doing better in the 1st Order questions for the Other Referent perspective (median = 83.33) compared to 1st Order questions for the Other referent condition (median = 66.67). There was also a significant difference between the Self Referent, 2nd Order and Other Referent, 1st Order Conditions ($Z = -4.42$, $p < 0.001$, $r = 0.72$), with patients having higher scores in the Other referent, 1st Order questions (median = 83.33) compared to the Other Referent, 1st Order questions (median = 50). There were no other meaningful significant interactions between conditions (all p 's > 0.62).

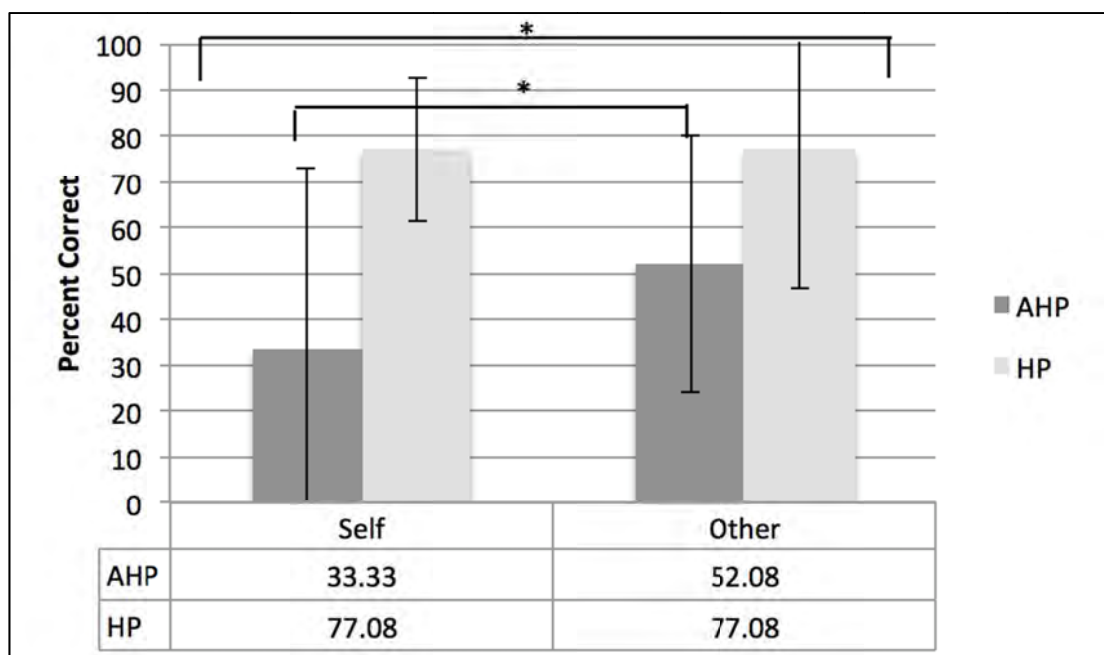


Figure 5.4 Percentage of correct response for self referent and other referent disability related ToM stories.

Note: Medians and interquartile range

5.5.6 Case study analysis

Previous studies (Marcel et al., 2004; Moro et al., 2011) have shown that there were individual differences in scores within groups when looking at differences in self and other referent awareness ratings. Therefore, in addition to the above group analysis, it was important to qualitatively investigate specifically how many AHP patients and to what extent they performed better in the other referent ToM stories compared to the self referent stories. This was done by calculating the difference between the self and other referent scores and looking at this difference on a case-by-case basis. Using this differential score, 63% (12 out of 19 AHP patients) had a difference of more than 25% (range: 25 - 58.3%) in performance in self and other referent stories. Of the remaining patients, three AHP patients did better on other referent stories (differential range: 4.17 - 16.6%) and three AHP patients performed better on self referent stories. Accordingly, 79% of AHP patients (15 out of 19 AHP patients) performed better in the other referent stories.

5.5.7 Lesion mapping results

Lesion overlay

Group-level percentage lesion overlay maps for the AHP group ($n = 19$) identified involvement of the fronto-parietal cortices with lesions extending into the temporal cortex. Lesions involved cortical areas and more focal subcortical areas, extending to dorsal frontal white matter (Figure 5.5A). The HP group ($n = 19$) in comparison presented with damage mostly around frontal and parietal areas, involving both subcortical and cortical regions (Figure 5.5B). Lesion volume (in cubic centimetres) was comparable between the AHP (mean = 11.05, SD = 12.91) and the HP group (mean = 5.94, SD = 7.88; $t(30) = -1.47$, $p = 0.15$). Subtraction maps identified clusters around the putamen, head of the caudate and insula ribbon, as well as the superior temporal gyrus (STG) and internal capsule (Figure 5.5C).

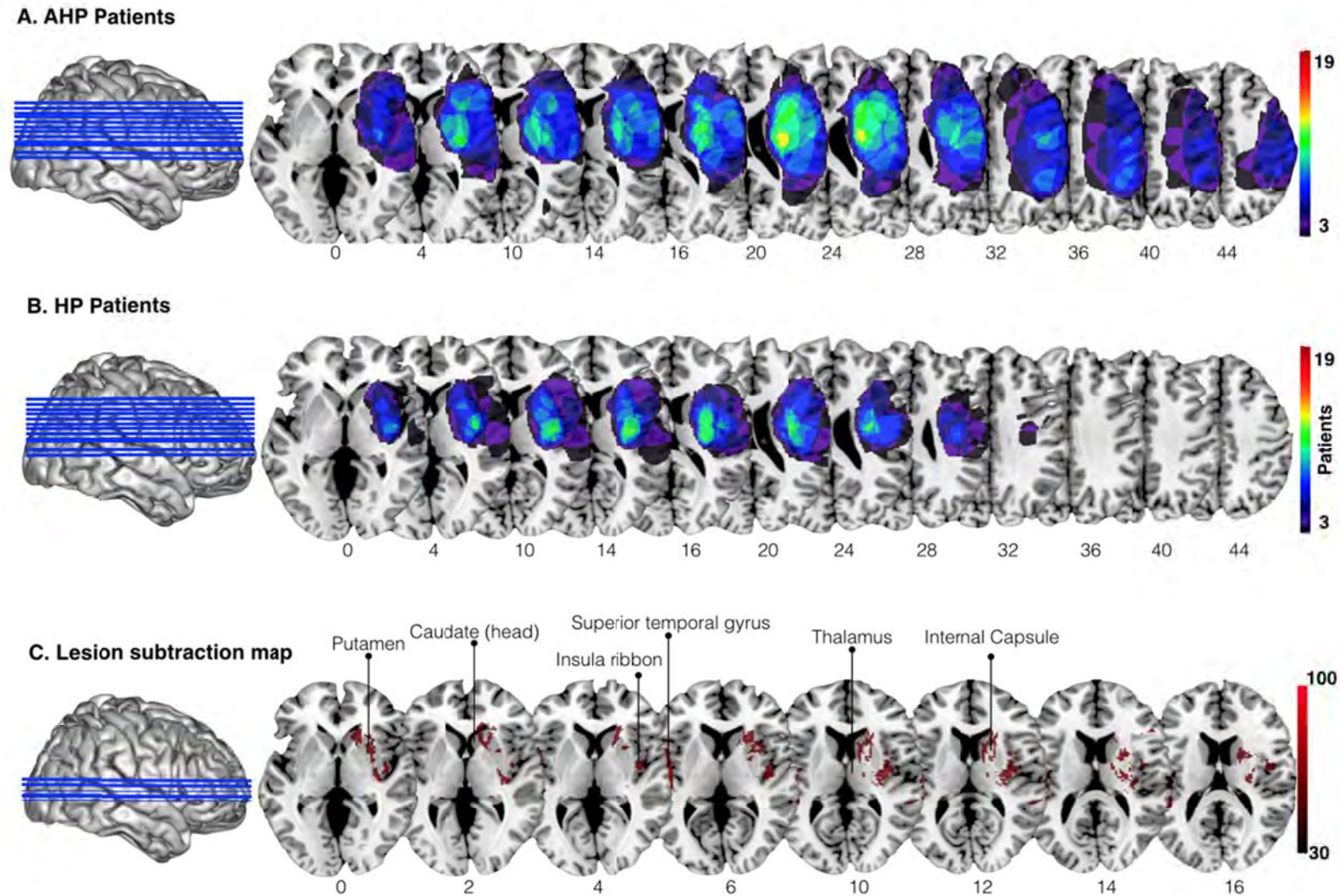


Figure 5.5 Group-level overlay maps for anosognosia for hemiplegia (AHP) patients and hemiplegic (HP) control patients

Note: **A.** Overlay lesions in AHP patients ($n = 19$); **B.** Overlay of HP patients ($n = 19$); **C.** Statistical analysis comparing the two patient populations (AHP – HP; results are corrected for multiple comparisons, $p < 0.05$ for $Z > 1.3$).

Voxel-based lesion symptom mapping (VLSM)

VLSM analysis using the continuous Feinberg awareness scores revealed that voxels within the STG, inferior frontal gyrus (IFG), insula ribbon and dorsal frontal white matter, as well as the middle frontal gyrus (MFG), supramarginal, postcentral and angular gyrus, were significantly associated ($p < 0.05$) with motor unawareness (Figure 5.6A). VLSM analysis looking at the differential score (other - self) in the disability ToM stories identified significant voxels ($p < 0.05$) within the IFG, STG, insula ribbon, caudate, putamen, thalamus and internal and external capsule, as well as dorsal frontal white matter (Figure 5.6B).

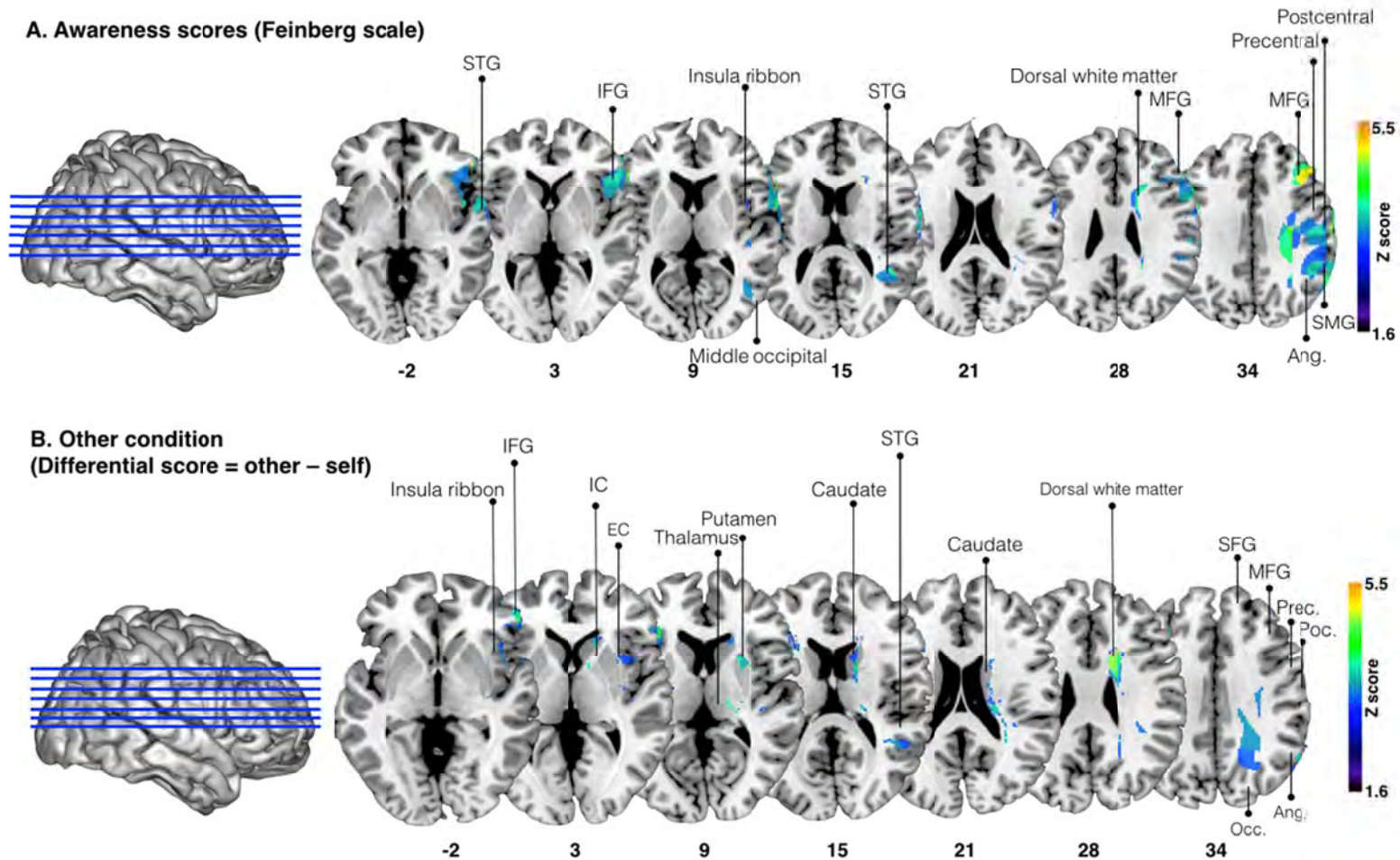


Figure 5.6 Voxel-based lesion symptom mapping (VLSM) analysis for Feinberg scale and difference in self and other referent scores for disability related ToM tasks

Note: **A.** Damaged voxels predicting the severity of unawareness of symptom deficit (Feinberg scale, inverted, continuous measure; $p < .05$ for $Z > 1.6$). **B.** Damaged voxels predicting the difference in self and other referent scores (differential score = other – self) in disability related ToM stories (continuous measure, $p < .05$ for $Z > 1.6$).

STG = superior temporal gyrus; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SMG = supramarginal gyrus; Ang = angular gyrus; IC = internal capsule; EC = external capsule; SFG = superior frontal gyrus; Prec = precentral; Poc = postcentral; Occ = occipital.

5.6 Discussion

The experiments described in this chapter examined the partiality of anosognosia (i.e. if patients have partial knowledge of motor deficits or “if unawareness of deficit is less than total” Marcel et al., 2004, pg. 20). Accordingly, three experimental studies were conducted in order to examine: (1) if there is a difference in motor awareness when asked from a 1st PP versus 3rd PP; and (2) if motor unawareness extended to the motor deficits of other patients and (3) if there is a difference in other referent awareness when asked from a 1st versus 3rd PP; and lastly (4) if there is a difference in the severity of unawareness in self referent versus other referent condition. The main behavioural findings were that AHP patients were more aware of their own paralysis when asked from a 3rd PP (the physiotherapists perspective) compared to a 1st PP (Experiment 1). AHP patients were also significantly more unaware of the paralysis of a ‘stooge’ patient shown in a video compared to HP controls. However there was no difference in other referent awareness when asked from a 1st versus 3rd PP; this may have been due to the overall low scores, which did not allow for enough variance between conditions (Experiment 2). Lastly, AHP patients performed better in other referent ToM stories than in self referent ToM stories, therefore being more aware of the others character’s motor deficits in the story than their own (Experiment 3). The main finding of our analysis combining behavioural and lesion data was that lesions to the IFG, STG, insula ribbon, as well as subcortical areas (i.e. the thalamus, putamen and caudate) and dorsal frontal white matter, were associated with the difference between other and self referent scores in the disability related ToM stories.

In line with Ramachandran & Rogers-Ramachandran (1996) case-series study, as well as Marcel et al. (2004) and Moro and colleagues (2011) results, this study has shown that at least in some AHP patients motor unawareness generalises or extends to include the paralysis of other patients. Nonetheless, although motor unawareness does extend in some cases, this is the first study to experimentally demonstrate that AHP patients are in fact less anosognosic for the other compared to the self. This difference in the degree of unawareness is directly shown in Experiment 3. The individual (case-study) analysis also confirmed that most AHP patients were more aware of the disabilities of the other hemiplegic patient in the ToM stories and less aware of their own disabilities in the self referent stories. The same pattern of results are observed when comparing Experiment 1 and Experiment 2 indirectly. Direct comparison is not possible because Experiment 2

entails video viewing (offline) whereas Experiment 1 entails a ‘live’ (on-line) interview. Future studies could film patients from a 1st versus a 3rd person perspective to create comparable data. Importantly, in previous group studies (e.g. Marcel et al., 2004; Moro et al., 2011) and the current study, individual (case-study) analysis was conducted in addition to group statistics. In all cases, results demonstrated that although most AHP patients showed an improvement in awareness for other referent questions, this is not the case for all patients. In the current study, three of the 19 patients showed a trend in the opposite direction –performing better in self referent awareness questions. Therefore the question arises as to why this effect does not apply to all anosognosic patients. One hypothesis could be that damage to different brain areas or the extent of the lesion (i.e. lesion size) could lead to a difference in self and other referent awareness (see Fotopoulou et al., 2010). An alternative suggestion being that co-occurring neuropsychological impairments, such as mental flexibility or general cognitive functioning, could lead to a difference in effect (see Marcel et al., 2004; Vocat et al., 2010).

Additionally, mirror and video feedback provides a 3rd person *visual* perspective that has been shown to restore motor awareness and body ownership (Fotopoulou et al., 2009; Jenkinson et al., 2011). Comparatively the results of the present study demonstrate that 3rd person *verbal* feedback can also result in an increase in motor awareness in AHP. Here, patients perceive their motor deficits through the 3rd PP of the physiotherapist objectively rather than through a 1st person, subjective perspective. Similarly in confabulating patients, discussions in the 3rd person were an effective strategy when confronting potentially negative or disability related themes (Fotopoulou, 2008). However, in comparing results from Chapter 4 and this current study, at first glance, there appears to be an inconsistency found in AHP patients’ ability to use the 3rd person perspective. However, results from Chapter 4 do not demonstrate AHP patient’s ability to adopt the perspective of another person, nor the ability to integrate such perspectives. It simply demonstrates that they have a deficit in 3rd person perspective taking. In the current study, the ability to spontaneously take on the ‘other’ perspective is again not tested here, but rather examined each perspective separately, and found that anosognosic patients are more aware in the 3rd person perspective. Furthermore, the difference found in 3rd person perspective taking in general ToM stories (Chapter 4) and other referent disability related ToM stories (Experiment 3) may be attributed to the *content* of the questions or stories. In the context of negative, disability related information, AHP patients may be emotionally driven or motivated to view themselves from the perspective of the other. However future

studies will have to directly investigate whether unaware patients have the ability to adopt a 3rd person perspective spontaneously.

Undoubtedly these findings also relate to literature on action observation and the mirror neuron system, initially discovered in the macaque monkey (Gallese, Fadiga, Fogassi & Rizzolatti, 1996). The human mirror neuron system has been shown to comprise of the inferior frontal cortex and inferior parietal lobe and is typically associated with imitation behaviour (Iacoboni, 2005) and social cognition (Iacoboni et al., 2005). The right lateralised mirror neuron system, which strikingly overlaps with the right frontoparietal network, is said to be involved in mapping other-to-self representations through motor simulation mechanisms and is essential to understanding a multimodal view of the embodied self (Uddin et al., 2007). Furthermore a simulation account of this action observation system has been widely suggested, proposing that when we see another persons actions or emotional responses we automatically project these responses onto our own actions, cognition or emotions (Gallese, 2003). The results of video viewing of the other hemiplegic patient in Experiment 2 may be closely related to this simulation account of action observation. Although AHP patients were still more unaware of the motor deficits of the patient in the video compared to HP controls, in comparison to the self referent task in Experiment 1 anosognosic patients showed less unawareness for the other compared to the self. Therefore it can be argued that offline video viewing of another paralysed patients actions (or lack of movement in this case) is automatically projected to the patient's own understanding of their motor abilities through the mirror neuron system. However, motor observation was not directly tested in this current study and therefore the above interpretations needs to be investigated by future research.

The lesion mapping results of our current study have also shown that this difference in self and other awareness in disability related ToM stories is associated with specific brain areas that are comparable to those of Moro et al. (2011). VLSM analysis found a relationship between differences in self and other awareness and damage around the dorsal frontal areas (IFG) extending to the temporal lobe (STG), and also includes subcortical areas (i.e. the thalamus, putamen and caudate) and dorsal frontal white matter. The ability to distinguish the self from the other, which has been shown in these behavioural results, has similarly been associated with right frontal and motor areas, particularly the IFG (Abu-Akel & Shamay-Tsoory, 2011; Keenan, Nelson, O' Connor & Pascual-Leone, 2001). Impaired performance on the ToM stories in general may also be

attributed to damage around the STG, which has been typically associated with mentalising and ToM abilities (Koster-Hale & Sax, 2013; see Chapter 4 for details).

Brain damaged areas associated with AHP in general were also investigated showing consistent results with the previous VLSM results in Chapter 3 and Chapter 4. Consistent with previous studies (see Vocat et al., 2010 and Fotopoulou et al., 2010) VLSM analysis using Feinberg awareness scores identified lesions to the insula Ribbon (Karneth et al., 2005) and premotor areas, specifically the IFG and MFG (Berti et al., 2005). Damage to temporal and parietal regions were also associated with unawareness, including the supramarginal and angular gyrus, areas that are known to be associated with social cognition (see Koster-Hale & Sax, 2013). Unfortunately, this lesion mapping approach cannot precisely identify the specific white matter tracts damaged in AHP patients and associated with awareness scores. However, damage to dorsal frontal white matter more generally is highlighted in the present study (see Chapters 3 and 4) and confirmed in previous papers (Fotopoulou et al., 2010; Moro et al., 2011).

5.1 Limitations and conclusion

It is also important to identify several limitations of the current study. The interpretations of the neuroimaging results are only tentative in nature, due to the inherent limitations of the lesion mapping approach and use of low resolution clinical scans. However, previous studies (e.g. Berti et al., 2005; Karnath et al., 2005; Vocat et al., 2010) investigating the anatomical correlates of AHP are all subject to the same limitations. An advantage of this current study was the use of the VLSM approach, which allowed for a direct statistical comparison between lesion and behavioural data. Future studies should try and acquire better quality structural scans to enhance the reliability of lesion findings. In regards to Experiment 1 and 2 there was no control for the floor effects in the HP group given the unique nature of anosognosia. However the same pattern of results was observed in Experiment 3, which was not affected by floor effects. Moreover, behavioural results from Experiment 3 are limited by the use of non-validated ToM stories. However, disability related ToM stories were based on previously validated measures, as well as being piloted on neurological patients. Additionally, although disability related ToM stories allowed for a direct comparison between self and other referent awareness, this is still in the context of a ToM question. Therefore is it not possible to distinguish exactly which errors were made due to general ToM impairments found in both groups and which errors can be attributed to self and other referent differences. These results do however

confirm the results in Chapter 4, showing that right-hemisphere damaged patients (both AHP and HP patients) have general deficits in ToM stories. Future studies are needed to directly compare differences in self versus other referent perspective taking, using another research paradigm, to disentangle the ToM and partiality of awareness results.

Overall, this study has provided experimental evidence suggesting that AHP patients do have partial awareness of paralysis depending on if they observe their disabilities from a 1st versus a 3rd person perspective, and if the information relates to themselves or to that of another person. Future studies are needed to not only further specify the specificity of the differences found in partiality of motor awareness, but also investigate the other clinical varieties in the presentation of AHP, such as the degree or severity of anosognosic behaviours.

Chapter 6 Towards rehabilitation: self-observation in video replay improves motor awareness

6.1 Introduction

Anosognosia for hemiplegia (AHP) is often a transient phenomenon with spontaneous recovery occurring within days or weeks from onset (Vocat et al., 2010). However, the presence of AHP in the acute stage may significantly obstruct rehabilitation efforts and consequently impede long-term functional outcomes (Gialanella, et al., 2005; Jehkonen et al., 2006). Specifically, patients with unawareness symptoms may refuse treatments that considerably improve prognosis (Di Legge, Fang, Saposnik & Hachinski, 2005; Cherney, 2006), may not take appropriate safety measures (Hartman-Maier, Soroker & Katz, 2001; Hartman-Maier, Soroker, Ring & Katz, 2002) and may not be realistic about their rehabilitation, housing, social and financial needs (Orfei et al., 2007; Prigatano & Morrone-Strupinsky, 2010). Thus, unawareness at the acute stage is linked to longer hospital stays (Maeshima et al., 1997), less likelihood of independent living (Pedersen, Jorgensen, Nakayama, Raaschou & Olsen, 1996), lower scores on measures of functional recovery (Gialanella et al., 2005; Maeshima et al., 1997) and activities of daily living (ADL; Maeshima et al., 1997). In fact, the impact of unawareness on ADL and functional outcomes is significant even when controlling for the extent of other cognitive deficits (Hartman-Maier et al., 2001). Thus, motor unawareness in acute stages is a specific, negative prognostic sign, compromising the course of recovery and rehabilitation and rendering the reintegration of these patients labour-intensive and costly. Moreover, it has been suggested that approximately 30% of AHP patients remain unaware of their motor deficits beyond the acute (<4 months) stage (Pia et al., 2004; Orfei et al., 2007). Thus, the rehabilitation of AHP in the acute and chronic stage can be of long-term therapeutic significance.

Recently some progress has been made in the management and rehabilitation of AHP (Kortte & Hillis, 2011; see Prigatano & Morrone-Strupinsky, 2010 and Jenkinson et al., 2011, for review). Nevertheless, to date no evidence-based treatment exists. Remission of AHP has been long reported using vestibular stimulation but unfortunately the effects of the stimulation are only temporary (Cappa et al., 1987). Transient improvement of awareness and neglect has also more recently been noted using a combination of treatments (Beschin et al., 2012). Beschin and colleagues investigated the effect of three treatment techniques that have traditionally been shown to temporarily improve neglect

(optokinetic stimulation, prism adaptation and transcutaneous electric nerve stimulation) in five patients with both anosognosia and neglect. Both left and right hemisphere damaged patients were included and were recruited 50 to 70 days post onset. The results indicated that patients responded differently to the same treatment, with anosognosia and not neglect temporarily improving with one patient, and only neglect improving with two other patients. Furthermore, in an extensive review of rehabilitation efforts in AHP, Prigatano and Morrene-Stupinsky (2010) outlined some practical guidelines for the management of unaware patients. Firstly, the severity, ‘types’ of AHP and the associated neurological and neuropsychological deficits should be clearly determined. Good rapport with both the patient and the family should then be established. Lastly, they suggest that a detailed and individualised rehabilitation plan should be developed (also see Jenkinson et al., 2011).

Aside from these more general intervention programmes, the first, specific, psychophysical intervention able to lead to a lasting remission of AHP was reported in a recent single case study (Fotopoulou et al., 2009). Fotopoulou and colleagues used video replay to provide an AHP patient with visual feedback of her paralysis from a ‘3rd person perspective’ (from the outside) and ‘off-line’ (at a time different than the one in which she initiated the movement). Patients with AHP, including the patient described in the Fotopoulou and colleagues’ paper, typically remain anosognosic when their paralysed arm is brought to their ipsilateral visual field and their paralysis is demonstrated. By contrast, by providing a video-based feedback the authors noted a dramatic increase of motor awareness in this patient. Crucially, the effect was recorded immediately after the intervention and lasted at one-month follow-up.

As some patients with AHP may show greater awareness in 3rd than 1st person verbal perspective taking tasks (Marcel et al., 2004; also see Chapter 5), the authors hypothesised that the 3rd-person perspective video-viewing may have facilitated the updating of the patient’s motor awareness. In addition, given the off-line nature of video replays, the fact that the patients motor intentions were not relevant at the time of video observation, may have facilitated awareness according to motor monitoring explanations (Berti et al., 2005; Fotopoulou et al., 2008). The aim of the current study was not to investigate these potential explanations of the effect but rather to examine the feasibility, effectiveness and optimisation of this video intervention protocol in further patients of different demographic, medical characteristics, and at different stages post-onset. Thus,

while using a general video intervention protocol, two variations of the original video-based methodology were developed and applied to the rehabilitation of two patients with severe AHP.

Indeed, Fotopoulou and colleagues (2009) applied this video intervention for the first time, but their patient was in the acute phase and her improvement was complete and immediate. Nevertheless, the authors admitted that the eventuality of a spontaneous recovery was not excluded, as the interval between onset and the intervention was very short. There is therefore a need to test the video intervention with chronic patients to address this issue of spontaneous recovery, as well as because a third of AHP patients remain anosognosic beyond the acute stage (Pia et al., 2004). However, this aim applies in parallel to the aim of testing the potential feasibility and effectiveness of the video intervention in acute settings, as the highest incidents of anosognosia are reported in the acute stage (Vocat et al., 2010) with important clinical, long-term implications as outlined above. Moreover, the feasibility and effectiveness of important, additional components of the basic video intervention protocol as necessitated by certain patients in certain acute settings (e.g. lower limb mirroring, emotional support) have still not been tested with acute patients. Therefore, the effectiveness and feasibility of this intervention in both acute and chronic patients merits further investigation.

Accordingly, in the first case (an elderly woman at the acute stage of recovery following stroke), a video replay and emotional support protocol was used in multiple intervention sessions targeting unawareness of both upper and lower limb hemiplegia and their functional consequences. On the basis of the aforementioned case report (Fotopoulou et al., 2009), the video intervention initially targeted only the left upper limb (LUL) and it was expected that viewing oneself unable to move one's arm would have led to a more generalised awareness of paralysis for both her left arm and leg. However, unlike the 2009 case study, the awareness recovery did not generalise to increased awareness for left leg movements. Therefore, both the LUL and the left lower limb (LLL) were targeted in separate, successive sessions, covering a period of 58 days.

In the second case, a younger man at the chronic stage of recovery following stroke participated to a single session of the video intervention, which in this case included two different conditions, a self referent and an other referent condition, both including questions that targeted awareness about both upper and lower limbs. The 'self referent'

video clip showed the patient himself in a video replay, while the ‘other referent’ video clip showed a video of another hemiplegic patient, age and gender matched, but without anosognosia. Both self-and-other videos were shown on the same day, 89 days post stroke, and the effects of this single session video intervention were monitored at different time intervals, with specialised awareness interviews targeting both upper and lower limb motor awareness. The two case studies are presented in turn below.

6.2 General methods

The two video interventions were an extension of the original aforementioned methodology (Fotopoulou et al., 2009) and they were conducted in one acute stroke ward and one rehabilitation clinic. Both the patients presented with severe AHP (see below for formal assessments) and were recruited based on the inclusion criteria described in Chapter 2. The general method of the video intervention protocol used in both the case studies included five specific research phases (for a schematic representation see Figure 6.1). The aim of this study was to extend the original Fotopoulou et al. (2009) approach, by examining the feasibility, optimisation and effectiveness of video-replay by: (1) testing both patient’s unawareness several times before the video replay intervention in order to show the stability of the symptom in both patients before the intervention; (2) applying this rehabilitation approach to two patients, in the sub-acute and chronic phases respectively, showing that the improvement was specifically due to the intervention, and not explained by spontaneous recovery, and to test the possibility and effectiveness of rehabilitation of AHP in both the acute and chronic stage; (3) introducing two new elements that are experimentally investigated, firstly the possibility to have specific and separate interventions for unawareness of upper and lower limb motor weakness; and secondly, the visual comparison with another patient as a possible instrument to enhance awareness of their motor weakness.

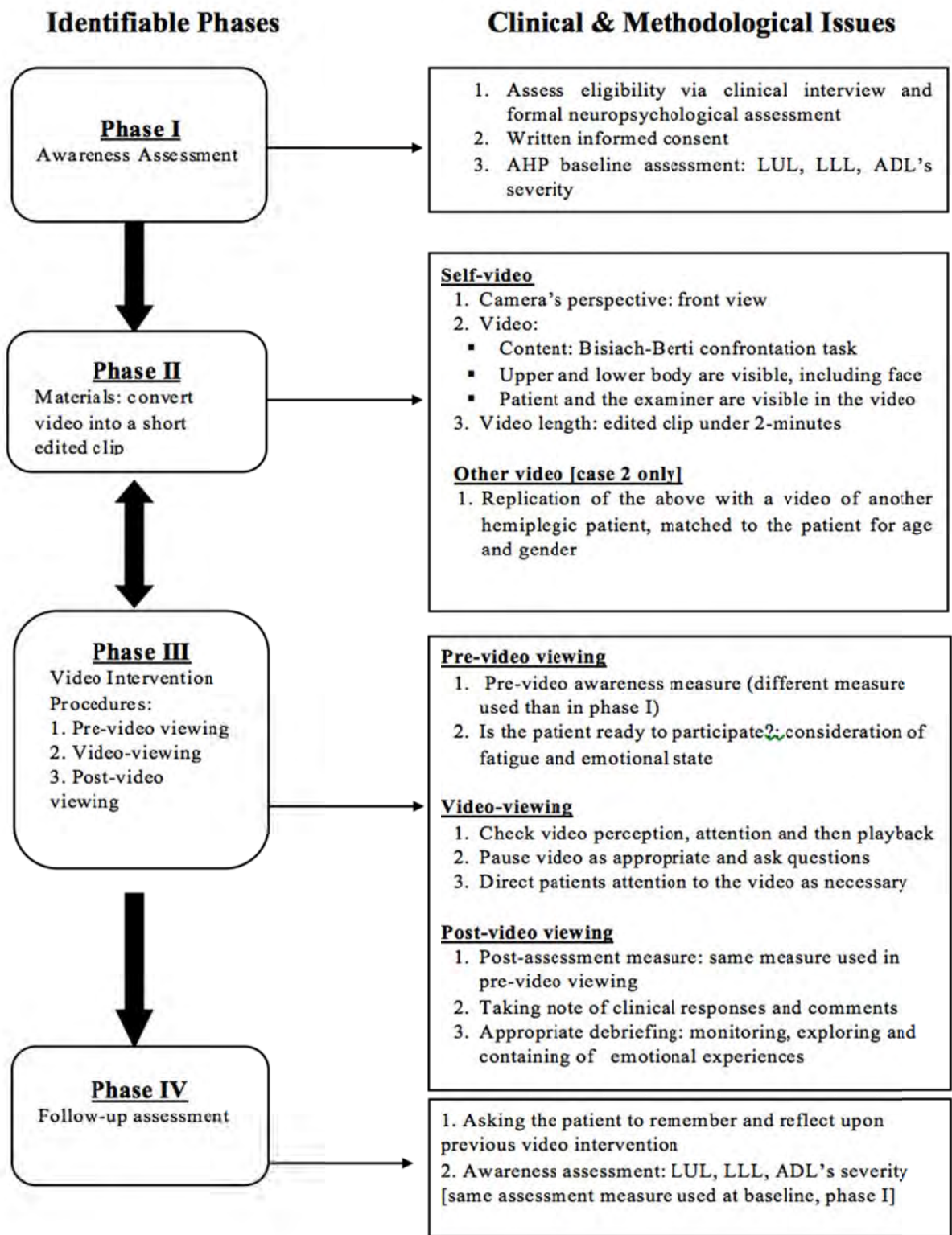


Figure 6.1 *Identifiable phases in the video replay intervention methods*

Note: Specific indications useful to employ and implement the video-intervention methodology are reported for each of the four phases of the training.

6.3 Case study 1

ED was an 88 year-old right-handed woman, a retired factory worker, with 10 years of education. She was previously mobile and independent, but with a medical history of ischemic heart disease and hypertension. ED was found collapsed with severe left-sided weakness and admitted to hospital. Radiology reports confirmed a dense right embolic middle cerebral artery (MCA) stroke. Figure 6.2 illustrates the lesion of the patient as documented in the clinical CT scan. The patient's lesion mainly involved the territory of the right middle cerebral artery, in particular the parietal and temporal cortex, insula cortex, and right precentral and rolandic operculum. The damage also extended to white matter tracts particularly the superior longitudinal fasciculus.

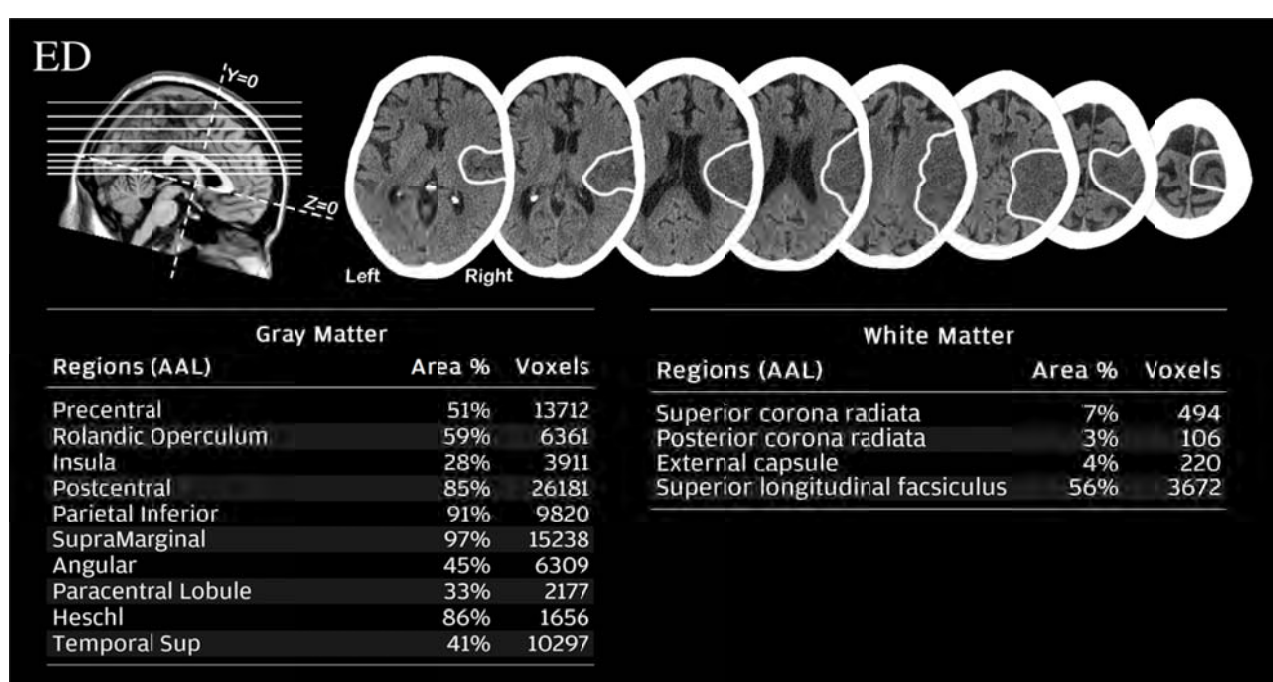


Figure 6.2 Neuroimaging examinations with white boundary lesion demarcation for patient ED's CT scan

Note: Right hemisphere is on the right side. The tables show the percentage of lesioned tissue affected by the lesion in the grey (left tables) and white (right tables) matter.

On admission, neurological examination confirmed left-sided hemiplegia (0/5 power in left limbs on Medical Research Council-MRC-Scale) and tactile loss. She also presented with dysarthria, left hemispatial neglect and hemianopsia. On initial assessment, 7 days following her stroke, ED was oriented to person, place and year, with some confusion as to the exact month. She was initially very fatigued but still cooperative. Mild decline in working memory was tested by her digit span. Formal neuropsychological assessment in the second week following onset (see Table 6.1 for full details; scores below the cut-off

are in bold) revealed impairment in executive functions (lack of fluency & concrete thinking), but showed only small motor perseveration and mild disinhibition. She also showed personal and extrapersonal neglect. Verbal and visual recall was poor to average, but consistent with age-appropriate memory decline. ED scored in normal range for depression and anxiety (Hospital Depression and Anxiety Scale).

Table 6.1 *ED's neurological and neuropsychological profile in repeated assessments*

| Function | Test | (maximum score) | Days from onset | |
|------------------------|---------------------------|-------------------------------|-----------------|---------------|
| | | | 7 | 58 post video |
| Awareness ^a | Feinberg | LUL (10) | 7* | 1 |
| | Berti | LUL (-2) | 2 | 0 |
| | | LLL (2) | 2 | 0 |
| Motricity | MRC ^b | Power LUL (5) | 0 | 1 |
| | | Power LLL (5) | 0 | 0 |
| Mood | HADS ^c | Depression (10) | 2 | Np |
| | | Anxiety (10) | 5 | np |
| Memory ^d | MOCA | Verbal recall | 3 | np |
| Working | | | | |
| Memory | Digit Span | Forwards | 5 | 6 |
| | | Backwards | 2 | 3 |
| Personal Neglect | Comb & Razor ^e | | -0.38 | np |
| Extra | BIT ^e | Star omissions | 50 | np |
| Personal Neglect | | Line bisection (3) | 0 | 1 |
| | | Line Crossing (40) | 5 | np |
| | | Copy (3) | 0 | 1 |
| Tactile | | | | |
| Extinction | Bisiach ^e | Upper limb | 3 | 1 |
| | | Lower limb | 3 | 2 |
| Visual | | | | |
| Extinction | Bisiach ^e | Upper visual field | 3 | 1 |
| | | Lower visual field | 3 | 1 |
| Executive | FAB ^f | Similarities | 1 | 1 |
| Functioning | | Lexical fluency | 1 | np |
| | | Motor Series | 2 | 2 |
| | | Go-no-Go (inhibitory control) | 2 | np |
| Left-Right orientation | | | 7 | 7 |

^aAwareness interview (Berti et al., 1996); AHP questionnaire (Feinberg et al., 2000)

^bMRC= Medical Research Council (Guarantors of Brain, 1986)

^cHADS=Hospital Anxiety and Depression scale, cut-off=8 points (Zigmond, A. S. & Snaith, R. P.,1983)

^dMOCA=The Montreal Cognitive Assessment (Nasreddine, 2005)

^eComb/Razor test (MacIntoch, Brodie, and Beschin, 2000); BIT= Behavioural Inattention Test (Wilson, Cockborn & Halligan, 1987); tactile and visual extinction= (Bisiach, Vallar, & Perani, 1986); ^fFAB= Frontal Assessment Battery (Dubois et al., 2000)

6.3.1 Overview of video intervention and timeline

The patient participated in a standard rehabilitation program of an acute stroke rehabilitation ward that mainly targeted the patient's mobility, daily living, housing and occupational needs. Video awareness intervention was the only neuropsychological intervention the patient received. The video intervention schedule was determined by the patient's hospital schedule, medical condition, emotional state and her willingness to participate in each session. Following the same, basic video-viewing procedures as in the original study (Fotopoulou et al., 2009), two video intervention sessions for awareness of upper limb paralysis (see below for details) were conducted in sessions scheduled 15 and 20 days post stroke. The awareness improvement about the upper limb did not generalised to awareness about the left leg paralysis. Thus, motor unawareness for the left leg paralysis was subsequently specifically targeted with a modified protocol (see below for details) in sessions scheduled 41, 42 and 57 days post stroke. Monitoring of AHP throughout the intervention period was achieved by stand-alone, awareness assessments (see below for details) carried out in sessions scheduled before, in-between and following the video intervention sessions at regular intervals.

6.3.2 Awareness assessment (Phase I, Figure 6.1)

Measures

AHP was assessed by two widely used measures, the Berti et al. (1996) interview and the Feinberg et al. (2000) scale described in Chapter 2. Feinberg et al. scale was also used as the pre-and-post measure during each video intervention session, as explained below. As the original Feinberg et al. scale addresses only the upper limb hemiplegia, a lower limb version was created as an additional measure for the second part of video intervention protocol (see below) by substituting 'left arm' for 'left leg' as needed, e.g. "Is your leg causing you any trouble?", "Please try and move your left leg for me. Did you move it?". As there are no norms for the Feinberg et al. interview, comparison data from a previous group study on AHP was used. Fotopoulou et al. (2010) tested a group of 7 patients with right-hemisphere damage, complete left sided hemiplegia and AHP (AHP group), and a control group of 7 patients with right-hemisphere damage, complete left side hemiplegia, but without AHP (HP group). The mean score of the AHP group was 5.64 (SD = 1.38) and of the HP group 0.98 (SD = 0.84).

Initial assessment results

On initial assessment, 7 days following the stroke, ED showed complete unawareness of her deficit, scoring 2 (maximum score) on the Berti et al. interview both for her left upper limb (LUL) and left lower limb (LLL) paralysis. In addition, she had a score of 7/10 on the original, upper limb Feinberg et al. scale. ED showed intractable false beliefs about her ability to move, but did not produce any florid confabulations or imaginary excuses when asked if she could move her limbs. Instead, she generally remained silent or avoided direct questioning during confrontational questions. For example, when asked if she could touch the examiners right hand with her left hand, she stated: *“I can move”*, but failed to execute the movement. When the examiner asked *“Did you move?”*, ED remained silent, then replied *“it is weak, but I can move it”*. When asked about her LLL weakness she was adamant that *“she has no problems”* walking. ED consistently reported that she *“feels alright”*, but she acknowledged medical opinion, saying *“The doctors tell me I have had a stroke, they must be right. I am not so sure, but the doctors are the experts, so I must have had a stroke”*, and consistently reported that she *“feels alright”*. Neurological reports, the physiotherapist and the nurse responsible for her care additionally confirmed the patients *“lack of insight”*.

6.3.3 Materials (Phase II, Figure 6.1)

On days 13 and 14 post stroke, ED consented to the Berti et al. interview to be repeated and filmed by the bedside on a portable digital video camera (Sony Handycam, DCR-SR57). Subsequently the film content was edited to create a 120 sec video clip showing the examiner standing on the left side of the screen, and the patient lying on the bed on the right side of the screen (her left side was on the right), with her torso being at a distance of approximately 1.5m from the camera. There was approximately 1m distance between patient and examiner. The patient was seen in front view with her upper body visible, including shoulders, arms, head and face. The edited clip contained awareness questions taken from the Berti et al. interview, including: a general question (e.g. *“Why are you here?”*), and two specific questions about the patient’s upper limbs (e.g. *“Can you move your left arm?”*) and two direct confrontations (e.g. *“Please try reaching my hand with you left hand. Have you done it?”*). The same edited video clip was used for both upper and lower limb video intervention, with an additional 50 secs added to the end of the clip when targeting left leg unawareness (i.e. total 170 sec clip). This later extra 50 sec clip was created by editing a filmed clip recorded on day 23 post stroke. This footage showed a direct view of ED sitting on her wheelchair, with her face, torso, upper and in

this case also lower limbs fully visible. The same questions from the Berti et al. interview were used, this time referring to the left leg. Questions also relating to ADL's (e.g. "Can you walk on our own/without help?" or "Can you get out of bed without help?" or "Can you go to the shops without help?") were also asked (Marcel et al., 2004).

6.3.4 Video intervention procedures (Phase III, Figure 6.1)

Pre-video viewing procedures

In each of the video intervention sessions the Feinberg et al. scale was first administered to ED as the pre-intervention awareness measure, including also the above mentioned questions relating to ADL's (Marcel et al., 2004). In the lower limb session the modified Feinberg et al. scale was used.

Subsequently, a laptop computer (screen size 13) was placed on a hospital table directly in front of the patient, 50 cm from her and, to exclude possible effects of neglect deficits, 20 cm right from the centre of her visual fields. In the first video intervention session (five days after the video as initially recorded), the patient was first shown the paused frame of the above-described video clip and was asked whether she was willing to view a video of herself trying to perform an action and discuss it with the examiner. She was informed of the procedure, the possibly upsetting content of the video and was given the opportunity to ask questions, discuss any aspects of the video intervention and choose to continue. In subsequent video interventions, in addition to these procedures, the patient was reminded of the previous assessments and video replays, and again asked whether she wanted to ask anything and whether she wanted to watch the video clip again. Although as in the original study (Fotopoulou et al., 2009) the patient and the examiner had already established good relationship during previous assessments, it was considered important to ensure in each session that the patient felt emotionally safe and comfortable in undergoing the assessment with the examiner (also see Fotopoulou, 2008). In addition, in each video intervention session, ED was first asked to describe what she saw in the paused frame (e.g. "Where are you in the video?") and to answer questions regarding the recognition of the identity of her own image (e.g. "Is that you in the video?"), body-parts discrimination and location, and left-right distinction (e.g. "Is that your left or right arm?").

Video-viewing procedures

The examiner made sure the patient's attention was drawn to the video and the aforementioned 120s edited video clip was played back. If the patient was distracted during video observation, the video clip was paused and her attention was redirected to the video. Halfway through the video, the clip was paused and the patient was asked the following two questions: "Can you see yourself trying to move in the video?" and "Did you move?". The same procedure was followed for left lower limb paralysis (day 41, 42 and 57), with the exception of the additional 50sec clip as described above.

Post-video viewing procedures

In each session, immediately following the video clip viewing, ED was asked the following set of questions: "Did you see yourself in the interview?", "What did you see?", and was given the opportunity to discuss her observations and feelings with the examiner. Subsequently, the Feinberg et al. scale was administered as the post-intervention awareness measure, including also the aforementioned questions relating to ADL's (Marcel et al., 2004). In the lower limb session the modified Feinberg et al scale was used.

6.3.5 Follow-up assessment (Phase IV Figure 6.1)

One month after the last awareness intervention, the Berti et al. interview and the Feinberg et al. scale (see above for normative data) were administered.

6.3.6 Results

Left upper limb video intervention

Prior to any video intervention sessions ED's anosognosia was severe and stable. In fact, in the four initial pre-intervention assessments (including the pre-intervention assessment of the first video session), her scores were one standard deviation (SD) or more above the mean of the aforementioned, comparison AHP group (Fotopoulou et al., 2010). Following the first video intervention, her awareness for her left arm paralysis improved (Feinberg et al. scale scores decreased from 8/10 to 4.5/10, see Figure 6.3). For the first time from her stroke, the patient commented that "*it is hard to move, and sometimes it is upsetting*". ED acknowledged her motor weakness, agreeing with the examiner that she had a stroke, and explained that she was fearful of losing the motor ability in her arms. ED appeared upset at this point and when the examiner asked why she was upset, ED

responded: “*You need your arms, don’t you?*”. ED then started to avoid further questions, making various excuses about everyday tasks she needed to complete. The examiner thus discontinued questioning and instead provided emotional support and eventually used distraction by discussion of positive topics from ED’s lifetime.

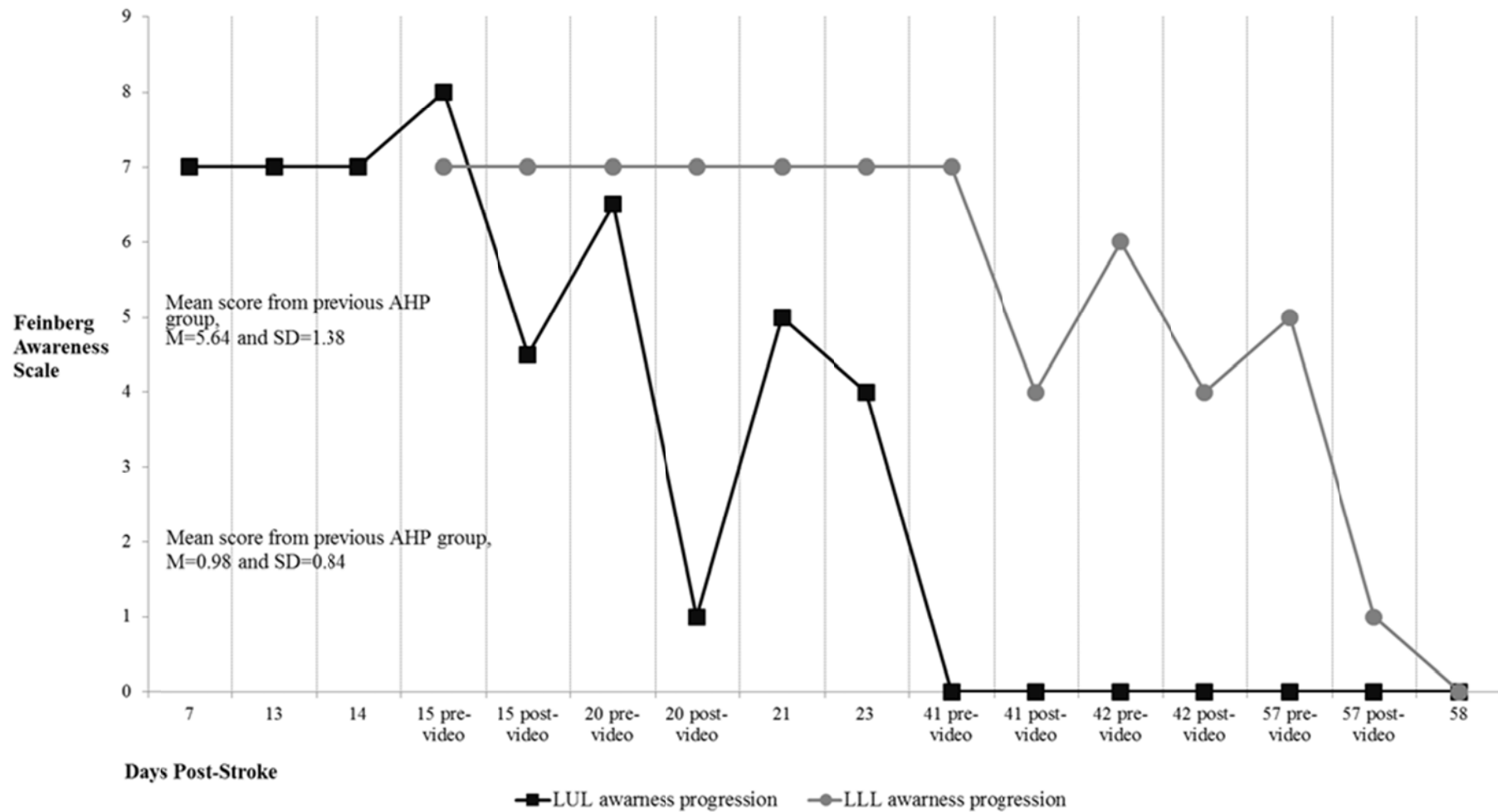


Figure 6.3 Left upper and lower limb awareness progression after self-observation using video replay in multiple intervention sessions

Note: The figure shows the awareness recovery for upper and lower limb paralysis over time. The original and adapted Feinberg et al. scale were used to acquire separate awareness scores for left upper limb (LUL) and left lower limb (LUL), respectively, before and after the intervention. Comparison data from previous right hemisphere groups with and without AHP on the original Feinberg et al. scale are also reported (Fotopoulou et al., 2010). The intervention led to a large decrease in unawareness in all sessions but awareness was not completely, nor permanently restored and a smaller increase of unawareness was noted between sessions, until total recovery was progressively achieved. Interventions targeting the arm had no effect on leg unawareness, which remained constant until it was specifically targeted by video-observation.

Five days later, ED's anosognosia had returned to pre-intervention levels with her scores falling within one SD above the comparison AHP patients' mean scores (Fotopoulou et al., 2010). Nevertheless, following the video intervention, ED showed a dramatic reinstatement of motor awareness on the Feinberg et al. scale (score 1/10) and began to cry at the end of it. The examiner inquired as to why she was crying, ED replied "*I feel sad because I can't move it*". The examiner then asked: "*What did you see in the video?*", ED: "*That I can't move my arm*". Examiner: "*What else did you see?*", ED: "*That I couldn't move my arm, I feel sad because I couldn't move it*". The patient went on to explain: "*I can't move on my own. I wish I could, but I can't.*" Emotional support was then provided to ED, including initially understanding her negative emotions and then reflecting on some of the positive possibilities her increased insight may allow in her general rehabilitation.

The following day an increase in her anosognosia scores was noted again (5/10 on the Feinberg et al. scale), but this score fell within one SD below the mean of the comparison AHP group (Fotopoulou et al., 2010). Moreover, in an informal conversation ED remembered the previous day's session and was able to describe her memories of gaining insight and having related emotions.

Left lower limb video intervention

Eighteen days later (41 days after her stroke) ED was less fatigued and more alert. Her anosognosia for upper limb paralysis had recovered (Feinberg et al. scale score 0/10). However, her anosognosia for lower limb hemiplegia seemed unaffected by both the video interventions and spontaneous recovery, scoring consistently more than one SD above the mean of the AHP comparison group (Fotopoulou et al., 2010) (see Figure 6.3). Moreover, she claimed that "*even with the stroke, I can still walk*". Accordingly, she rated herself as fully able in questions about bipedal tasks, especially walking (Marcel et al., 2004). Interestingly, upon confrontation ED did not present with illusionary movements (Feinberg et al., 2000; Fotopoulou et al., 2008) and attributed her failures (e.g. not being able to walk at the moment) to third parties: "*I can get out of this bed, but they put bars on to stop me*" or "*Yes I can walk, if they let me go out, I could walk*" or "*There is nothing wrong with my body, it's the chair*". ED was rather resistant and avoidant to questions relating to her LLL paralysis, frequently making excuses, apparently in order to stop related conversations.

Immediately following the first LLL video intervention at 41days post-onset, ED's anosognosia score on the modified Feinberg et al. scale decreased to 4/10. Towards the end of the assessment, when asked if she could get out of bed without help, ED replied "*No I can't, yet I think I can*". At this point, she appeared distressed and appealed to the examiner, remarking that if it was the examiner who could not walk, she would feel sadness for the examiner ("*It would make me feel sad if you couldn't walk, couldn't go anywhere on your own*"). The discussion continued in this emotional tone from both parties ensuring the patient's distress had been understood and contained, and the formal assessment was concluded.

The next day her scores concerning left lower limb paralysis awareness increased to 6/10 (modified Feinberg et al. scale). However, immediately following a second video intervention her scores declined again (4/10, corresponding to more than one SD below the mean of the AHP comparison group, Fotopoulou et al., 2010). Immediately after the interview the patient began to cry and asked the examiner: "*If I can't get out of this chair, what am I going to do?*". Again, the above described emotional support protocol was followed.

On the next follow-up assessment, the patient remembered the previous sessions but became increasingly distressed during recall. Accordingly, emotional support was offered to the patient, any sort of further confrontation was avoided and a two-week interval was left before the next video intervention. During this interval the patient's emotional state was monitored and supported in brief, informal visits.

Two weeks later, the third and last video intervention was administered. The patient did not show any evidence of anosognosia for upper limb paralysis, but her scores on the modified Feinberg et al. scale for lower limb paralysis was 5/10 (within one SD below the mean of the AHP comparison group, Fotopoulou et al., 2010). ED commented: "*I can stand, but I can't get out of this chair and I don't know why*". Following the video intervention, the interview showed a dramatic improvement in awareness (1/10 the modified Feinberg et al. scale). When the examiner asked: "*Can you walk on your own?*" ED remained silent for a while and hesitantly replied "*Maybe a little, but not without a walking stick*". The patient was mildly agitated but not tearful as in previous sessions. When asked, "*Can you move your left leg?*" ED replied, "*I don't think so*". The examiner then asked, "*Can you walk?*", ED said she was not able to and became upset. The above

emotional support protocol was administered and the patient and examiner discussed the possibilities and opportunities for future, practical support with everyday activities.

At another assessment the next day, 58 days post stroke, ED showed no evidence of anosognosia for both left upper and lower limb paralysis (0/10 LUL and 1/10 LLL, respectively). Furthermore, ED remembered the video interventions and was able to reflect on her general disabilities and the related negative emotions. The same results were noted in a final, follow-up assessment 82 days post stroke. These findings were further confirmed by administering the Berti et al. interview, in which the patient showed no sign of AHP (score =0/2).

6.4 Case study 2

FG was a 70 year-old right-handed man, a retired builder with 5 years of education. He suffered a large haemorrhagic stroke in the region of the right middle cerebral artery. Figure 6.4 illustrates the lesion of the patient as presented in the clinical CT scan. Lesioned areas mainly involved the basal ganglia structures and subcortical white matter (internal capsule, anterior, superior and posterior corona radiate, external capsule, superior longitudinal fasciculum and fronto-occipital fasciculum). Parts of the temporal, insular and frontal cortices were also damaged.

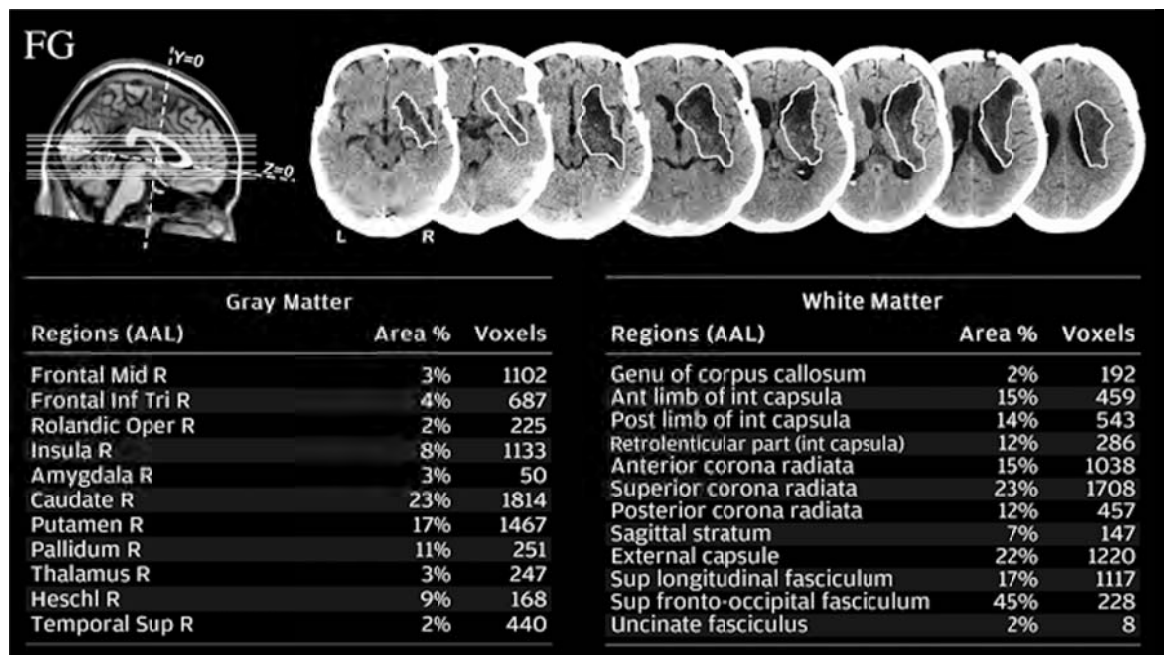


Figure 6.4 Neuroimaging examinations with white boundary lesion demarcation for patient FG's CT scan

Note: Right hemisphere is on the right side. The tables show the percentage of lesioned tissue affected by the lesion in the grey (left tables) and white (right tables) matter.

On initial examination, 72 days following the stroke, FG presented with complete left-sided hemiplegia (0/5 power in left upper and lower limb on MRC scale) and left hemispatial extrapersonal and personal neglect (see Table 6.2; scores below the cut-off are in bold). The patient was alert and oriented to person and place, but showed some confusion in time. Neuropsychological assessment further revealed important deficits in executive functions (Frontal Assessment Battery, FAB), but no impairments in verbal memory (i.e. story recall), language or general cognitive abilities (Mini-Mental State Examination, MMSE). There was no evidence of depression or anxiety in the Becks Depression Inventory.

FG presented with severe AHP, reporting that he had no motor deficits in his left arm and leg. Although FG did confirm that he was in the hospital for rehabilitation, he was adamant that he could move his left arm and leg with “no problems”. His only complaint was of pain in his back, neck and shoulders. He claimed to be in the hospital for further assessment of his back-pain, and maintained that the doctor had decided he should be hospitalised for rehabilitation training. When asked why he was sitting in a wheelchair, he responded that it was to help the nurses taking him to medical visits.

Table 6.2 *FG's neurological and neuropsychological profile in the pre- and post-training assessments*

| Function | Test | (maximum score) | Days from onset | Post video |
|------------------------|---------------------------|---------------------------|--------------------|------------|
| | | | 74 | 103 |
| Awareness ^a | Bisiach | LUL (3) | 3* | np |
| | | LLL (3) | 3 | Np |
| | VATA-m (Max=36) | Bimanual | 22 | 12 |
| | | Bipedal | 10 | 7 |
| | Marcel-Moro | Total score (23) | 20 | 8 |
| | Modified interview | General (2) | 2 | 2 |
| | | Upper Limb (9) | 7 | 3 |
| | | Lower Limb (8) | 7 | 1 |
| | | Daily life activities (4) | 4 | 2 |
| Motricity | MRC ^b | Power LUL (5) | 0 | 0 |
| | | Power LLL (5) | 0 | 0 |
| | | | | |
| Mood ^c | B.D.I. | | 5 | 8 |
| Memory ^d | Story Recall | | 12.08 | 12.07 |
| Working | | | | |
| Memory | Digit Span | Forwards | 4 | 4 |
| Personal | | | | |
| Neglect | Comb & Razor ^e | | -0.05 | -0.11 |
| Extra | BIT ^e | Stars omissions (46) | 42 | Np |
| Personal | | | | |
| Neglect | | Line bisection (9) | 0 | 3 |
| | | Line Crossing (40) | 9 | 11 |
| | | Copy (4) | 0 | 0 |
| | Tactile extinction | | 0 | 0 |
| | Visual extinction | | 0 | 0 |
| Executive | FAB ^f | Similarities | 1 | 3 |
| Functioning | | Lexial fluency | 1 | 2 |
| | | Motor Series | 2 | 1 |
| | | Go-no-Go | | |
| | | (inhibitory control) | 1 | 0 |
| General | | | | |
| Cognitive | MMSE ^g (30) | | 23.7 | Np |

^a Bisiach interview (Bisiach et al. 1986); VATA-m= Visual-Analogue Test for Anosognosia for motor impairments (Della Sala et al. 2009); Marcel-Moro modified interview (Moro et al., 2011)

^b MRC= Medical Research Council (Guarantors of Brain, 1986)

^c BDI= Becks Depression Inventory (Beck, Ward & Mendelson, (1961);

^d Story recall & digit span (Spinnler & Tognoni, 1987)

^e Comb/Razor test= test of personal neglect, bias is calculated according to MacIntoch et al. (2000); BIT= Behavioural Inattention Test (Wilson et al.,1987)

^f FAB= Frontal Assessment Battery (Apollonio et al., 2005)

^g MMSE= Mini-Mental State Examination (Folstein, Folstein & McHugh,1975)

6.4.1 Overview of intervention and timeline

The patient participated in a tailored rehabilitation program in an in-patient rehabilitation clinic. That program focused on his motor and neglect deficits. The video intervention was the first neuropsychological intervention the patient received for his AHP. In this patient, only one session of video intervention took place on day 89 post stroke. However, this was a “double” video session, in the sense that the viewing of a self-referent video clip as the one described in the previous case study, was followed by the viewing of a similar clip referring to another hemiplegic patient (‘other’ referent; see methods for details). Moreover, a specific “experimental” awareness task (see below) was applied as a pre-and-post awareness assessment measure on the day of the intervention. In addition, the same measure was applied on two other dates prior to the intervention day (72 and 82 post onset) and three other dates post intervention (90, 103 and 113 post stroke). In all post intervention assessments this experimental awareness task was administered twice, one with reference to the “*self-referent-clip*” and one with reference to the “*other-referent-clip*”. The intervention and assessment dates were determined by the patient’s hospital schedule, medical condition, emotional state and willingness to participate in each session.

6.4.2 Clinical awareness assessment (Phase I, Figure 6.1)

FG’s AHP was measured using three different methods (see Table 6.2): (1) the 4-point “Bisiach” interview (Bisiach et al., 1986); (2) the Visual-Analogue Test for Anosognosia for motor impairment (VATA-m; Della Sala et al., 2009); (3) the modified “Marcel” structured interview (Marcel et al., 2004; Moro et al., 2011). The Bisiach et al. interview uses a 4-point scale to evaluate the severity of the patient’s unawareness identified as mild, moderate or severe (0= aware, 1= mild unawareness, 2= moderate unawareness, 3= severe unawareness). The VATA-m is a measure of unawareness of motor deficits combining both the patient’s and caregiver’s evaluation of the patient’s motor abilities in a series of specific motor tasks (e.g. walking or drinking from a glass). A discrepancy score is then calculated with a maximum score of 36 (scores between 6.8 and 12.0 indicate mild anosognosia, scores between 12.1 and 24 indicate moderate unawareness, and scores between 24.1 and 36 indicate severe unawareness). In addition, a modified version of the Marcel structured interview (Marcel-Moro’s interview, Moro et al., 2011) was used. The interview consists of 23 questions (each of them scored as 0 = aware and 1 = unaware). The questions address four different aspects of awareness, namely: (i) general awareness of illness; (ii) awareness of sensory-motor abilities for upper limb; (iii)

awareness of sensory-motor abilities for lower limb; and (iv) awareness of abilities in ADL's.

In FG, no acknowledgement of the disorder could be obtained even after clear demonstrations of paralysis (scoring 3 on the Bisiach et al. interview). He also scored below the cut-off in the VATA-m, scoring 22 for bimanual and 10 for bipedal actions (both corresponding to severe AHP). During the modified Marcel-Moro's interview, FG rejected any evidence of his motor deficits and again claimed complete autonomy in his ADL's, scoring 20/23. In one instance during assessments, FG did admit to a certain degree of left upper limb weakness, but still continued to claim that he was "not paralysed".

6.4.3 Materials (Phase II, Figure 6.1)

On day 82 post stroke, FG consented to his awareness testing to be filmed using a portable digital video camera (JVC GR-DVL 150 E). The patient was recorded while being seated, with the examiner standing on his left side. There was approximately 1m distance between the patient and the examiner. A 120 sec video clip was subsequently edited from this filming session. The video clip showed the patient in front view, with FG's face and body, and both right and left upper and lower limb visible in the video. The edited clip contained general questions (e.g. "Why are you here?"), specific questions about the patient's limbs ("Can you move your left arm?"), and direct confrontation questions (e.g. "Please try reaching my hand with your left hand? Have you done it?") (as described in Fotopoulou et al., 2009). In the edited clip, when the patient was asked: "Can you move your left arm?", he replied that he was able to do so and then spontaneously moved only his right arm. At this point, the patient was asked to use his left hand to reach the examiner's hand. The patient claimed that he had performed this action and that he was confident in his reply. When asked to indicate which one was his left arm the patient used his right arm to reach across and indicate his left arm, suggesting he was not suffering from left-right confusion.

An identical interview to the one described above was conducted with another hemiplegic patient, matched for age and gender, who was however fully aware of his paralysis. This interview was recorded and edited resulting in a video clip as similar as possible in content and length to FG's edited clip described above. Of course, the patient's answers to the same questions were different, in the sense that he was aware of his paralysis. For

example, he reported to be at hospital because of his paralysis; he agreed that he was not able to move his left arm and leg, and, after the confrontation task, he recognised that he did not successfully reach the examiner hand.

6.4.4 Video intervention procedures (Phase III, Figure 6.1)

Pre-video viewing procedures

On two sessions prior to the day of the video intervention session, as well as on that day (89 days post stroke), an experimental measure of anosognosia, the Judgment of Actions Test (JAT, Moro et al., 2011), was used as a pre- and post- intervention awareness measure (see also below). The JAT tests the awareness of motor deficits in 23 separate and specific actions. The patient is asked to judge his or another person's ability to execute a series of unimanual, bimanual and bipedal actions (e.g. kicking a ball, climbing upstairs, picking up a glass). There are 23 questions, 10 of which refer to unimanual actions (UM, 5 for each hand), 8 to bimanual (BM) and 5 to bipedal (BP) actions (Moro et al., 2011). Right unimanual actions are considered as control questions for subject's comprehension and consistency. The patient is asked to judge his or another persons' motor abilities on each action, using an 11-point scale (from 0 = "I cannot do this action at all" to 10 = "I am completely able to do this action").

Video viewing procedures of self referent clip

Following the pre-intervention JAT task, a laptop computer (screen size 13') was placed on a table directly in front of the patient, 50 cm from him and 20 cm right from the centre of his visual fields, to minimize possible neglect confounds. The patient was informed of the procedure, and given the opportunity to ask any questions. As in the case above and the original study (Fotopoulou et al., 2009) there was a good therapeutic relationship already established between the patient and the examiner. The video replay took place approximately seven days after the video was initially recorded.

FG was first shown the video in pause mode and asked to identify himself in the video and discriminate between left and right body-parts (e.g. "Is that you in the video?", "Is that your right/left arm?"). The examiner confirmed that the patient was comfortable to continue and watch the video replay.

The clip was played back to the patient. He initially avoided directly looking at the video and the examiner gently guided his attention to the video clip. After the first 10 seconds the patient's attention focused on the video, although he occasionally and spontaneously shifted his attention from the video to the direct view of his left hand and back.

During the playback, general questions were first asked (e.g. "Where are you in the video?"). In the video after the patient was asked "Why are you here?", his response in the recorded video only acknowledged his back and neck pain, and no motor difficulties. At this point in the video clip, the video clip was paused and the examiner asked, "*Do you agree?*". FG responded: "*So, so, my arm and leg are not functioning very well, it is very bad actually*". The examiner then asked, "*What is?*", FG: "*I have to admit, the weakness is very bad*". Examiner: "*Can you walk?*", FG: "*No, I cannot*". At this point the video clip was restarted. While watching the confrontation task in the video (i.e. the patient is asked to move his left arm), the patient spontaneously remarked, "*I thought that I would have recovered better*". The video was paused again and the examiner then asked: "*How do you see yourself recovering now?*", FG: "*I have not recovered very much*". After the end of the video playback the examiner asked: "*Can you walk?*", FG answering, "*Not so good*". Examiner: "*Why?*", FG: "*My left leg is weak*". The examiner then asked: "*And can you lift it?*", FG replying: "*Yes, I can, but in the video the leg did not move.*" The JAT was subsequently administered.

Viewing procedures of other referent video clip

Thirty minutes after this self referent video intervention, the video referring to the other hemiplegic patient was played back in the same manner as the self referent video intervention. FG correctly identified that the person in the video was a hemiplegic patient ("*The man in the video can not move*"). During the confrontation task the video was paused and the examiner asked FG if the hemiplegic patient had managed to reach the examiners hand. He answered: "*No, it is impossible.*" FG made no other comments during the rest of the video. The JAT (referring to the other patient) was again administered directly following the end of the video as the post-intervention awareness measure. It was repeated in the self and other referent conditions the day after (90 days in Figure 5).

6.4.5 Follow-up assessment (Phase IV, Figure 6.1)

A follow-up assessment by means of the VATA-m and Marcel-Moro interview was conducted 14 days after the awareness intervention session (see Table 6.2). The JAT was also administered 24 days after the video session to monitor the patient's awareness (see Figure 6.5).

6.4.6 Statistical analyses

Statistical analysis was performed on the pre- and post-intervention JAT scores. Left unimanual (UM), bimanual (BM) and bipedal (BP) actions were analysed separately. Unimanual scores referring to the right hand were excluded from the analysis as the patient performed at ceiling, confirming intact attention and comprehension during these control trials. The self referent and other referent scores were also analysed separately, apart from one final self vs. other referent comparison applied to the post-video assessments only (there were no other referent pre-intervention assessments). The Friedman test was used to analyse any significant differences between the JAT three baseline assessments. Since there was no difference in these scores, the average of the three baseline scores was calculated and used as a global baseline measure.

For the *self referent video condition*, the mean baseline assessment score and the post-intervention scores were compared. For the *other referent video condition*, only the post-awareness assessment scores were compared. Lastly, for the self-other referent video comparison the results from all JAT evaluations were analysed, excluding the baseline measures. The Friedman rank sum test was used to verify if the observed improvement in awareness was statistically significant. If this test reached a statistical significance, the Wilcoxon tests for dependent data, with False Discovery Rate correction as post-hoc test, were used.

Finally, to check if there was a stepper trend in the recovery of awareness in the self referent or in the other referent condition, a simple ratio index was computed as a qualitative index. Regression linear models were used on JAT values for right UM, left UM, BM and BP for other referent and self referent conditions on all the post-video evaluations. Then, for each typology of score, the ratio between the slope of the self referent linear model and the slope of the other referent linear model was calculated (self angular coefficient/other angular coefficient). If this ratio index is more than 1, it means that the self referent awareness has a better improvement, while a ratio index lower than 1

indicates that the other referent awareness has a better improvement. Although this index is not thought to have a strong statistical validity (mainly because of the small amount of observations), it may be useful to show the differences in the trends of responses, which could be important for discussions on clinical outcomes.

6.4.7 Results

Self referent condition

Prior to any video intervention FG's anosognosia was severe and stable. As shown in Figure 6.5 no change in awareness was observed in the assessments prior to the video replay ($\chi^2_{(2)} = 3.07, p = 0.215$). All three pre-awareness assessments demonstrated severe anosognosia for left unimanual, bimanual and bipedal actions (see Figure 6.5). Following the video intervention, FG spontaneously remarked: "*We have to work hard*". When the examiner asked to what he was referring to, the patient explained that he needed to work hard on his rehabilitation, agreeing that he was not well and he was unable to move. The JAT scores immediately after the video intervention show an increase in awareness for motor deficits of unimanual left and bimanual actions (see Figure 6.5). Crucially, in the following assessments FG's trend of improvement seemed to continue particularly in LU and BM actions (see Figure 6.5).

This gradual improvement was significant in BM actions ($\chi^2_{(4)} = 13.01, p = 0.011$) and in LU actions ($\chi^2_{(4)} = 10.91, p = 0.028$), and showed a trend of significance in BP actions ($\chi^2_{(4)} = 8.74, p = 0.068$). Furthermore, the comparison between baseline and individual sessions shows that this gradual improvement becomes statistically significant in BM actions only in the follow-up sessions (post-hoc tests: baseline vs. 103 days: $W = 36, p = 0.028$; baseline vs. 113 days: $W = 33, p = 0.042$).

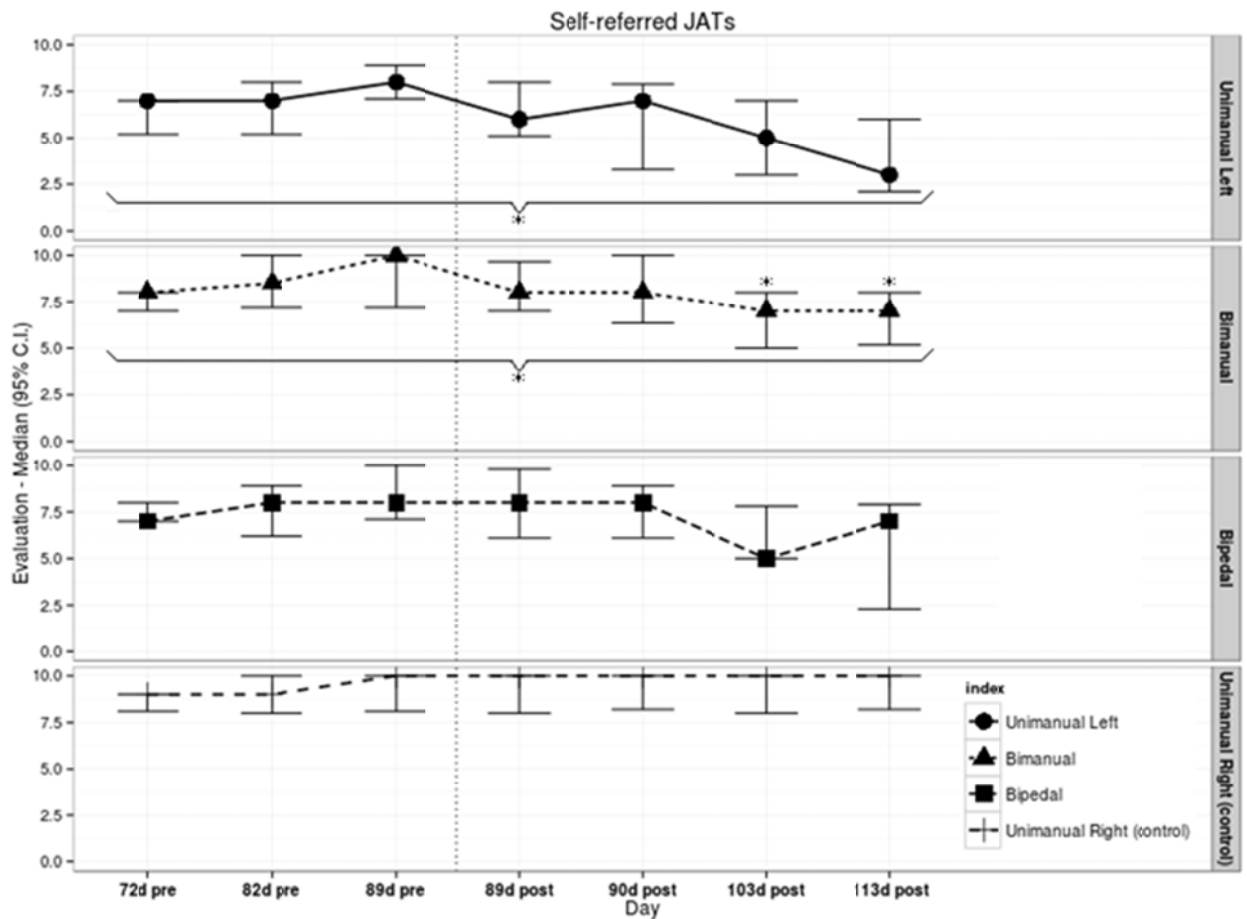


Figure 6.5 *Judgement of Actions Test (JAT) scores for self referent condition before and after video intervention*

Note: Median (95% Interval of Confidence, C.I.) values are shown for each condition and each observation. The three pre-video observations in the left side of the dotted vertical line were averaged to a unique baseline for statistical tests. Results show an improvement in awareness directly following the video replay, and become statistically significant at days 103-113, indicating a gradual process of awareness recovery.

The patient's improvement is additionally confirmed by clinical awareness assessment carried out 14 days after video replay, as shown by VATA-m (Della Sala et al., 2009) and Marcel-Moro's interview scores (103 days after stroke, in Table 6.2). Specifically bimanual VATA-m scores indicate that FG's anosognosia improved from severe to moderate following the intervention. The Marcel-Moro interview also indicated an improvement of anosognosia for lower limb paralysis, but this improvement was only partially confirmed by the VATA-m. Results of the neuropsychological assessment demonstrated that the improvement was specific to awareness scores as neither personal, nor extrapersonal neglect, nor executive functioning scores were modified post-intervention (see Table 6.2).

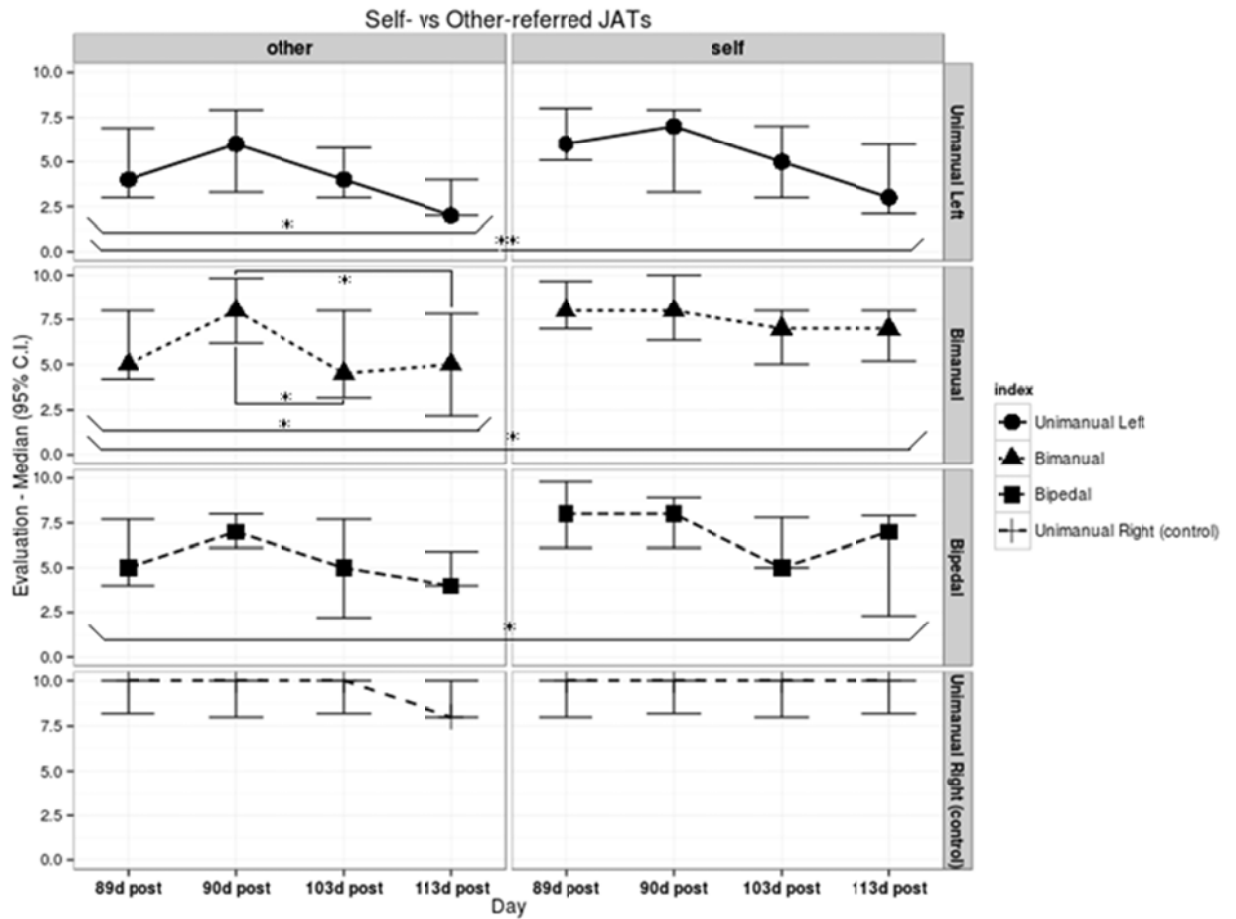


Figure 6.6 Comparison of self referent vs. other referent ratings on judgment of actions test (JAT)

Note: Median (95% C.I.) values are shown for each condition and each observation. Statistical significances are represented by brackets containing the self- and the other-referent distributions and are related to their overall comparison. Brackets underlying a single other-referent distribution represent a statistical significance in the overall trend.

Comparison self and other referent responses

FG's scores referred to the motor ability of the other patient (other referent) were significantly lower than the self referent scores (Figure 6.6). This indicates greater insight into the deficits observed in the other referent condition than the self referent condition. In comparison to self referent ratings, FG was better able to recognise the deficits of the 'other' hemiplegic patient in all the actions (BM: $\chi^2_{(1)} = 8.17, p = 0.004$; BP: $\chi^2_{(1)} = 5.4, p = 0.02$; LU: $\chi^2_{(1)} = 5.4, p = 0.02$), but not in RU action ($\chi^2_{(1)} = 0.2, p = 0.65$). Nevertheless, qualitatively ratio indexes between the slopes indicates better improvement in self referent condition for left UM (1.375, self slope = -1.1, other slope = -0.8), BM (1.14, self slope = -0.4, other slope = -0.35), BP (1.20, self slope = -0.6, other slope = -0.5) but not right UM (0, self slope = 0, other slope -0.6). Thus, although FG recognised the paralysis

in the other patient better than in himself, the trend of recovery induced by the video rehabilitation indicates a more specific effect in self referent condition. For clinical observations, statistical analysis and further results concerning the other referent condition, see Appendix O.

6.5 Discussion

This study presented two patients with severe anosognosia for hemiplegia following stroke in different post-onset stages (acute versus chronic) and found that self-observation in video replay contributed to the reinstatement of motor awareness in both cases. Both patients showed stable and severe AHP in several assessments prior to the intervention and both patients showed evidence of marked improvement in motor awareness following the intervention. Although the precise intervention protocols applied, as well as the pattern of the recovery observed were different between the two patients, these results suggest that in both cases the awareness improvement cannot be accounted exclusively by spontaneous recovery. This conclusion is more obvious in the case of the chronic patient, who had showed stable and severe AHP for more than two months post-onset. Additionally, there was no change found in neglect following the video-replay, suggesting that the change in awareness can therefore not be explained by a change in neglect. These results are discussed below, in the context of the wider literature on AHP.

AHP typically remits over time as a result of spontaneous recovery, but sometimes patients remain unaware also in the chronic stage (see Pia et al., 2004 for review). Moreover, the presence of AHP in the acute stage may significantly obstruct rehabilitation efforts and consequently impede long-term functional outcomes (Gialanella et al., 2005; Jehkonen et al., 2006). As outlined in the introduction, there have been recent advances in the management of AHP by providing specific rehabilitation guidelines and strategy's (see Prigatano & Morrene-Stupinsky, 2010 and Jenkinson et al., 2011 for reviews), with temporary remission of AHP also being recently reported using a combination of techniques (see Beschin et al., 2012). Unfortunately, despite these rehabilitation efforts, there is currently no known, effective intervention for permanent restoration of motor awareness in patients with AHP (Kortte & Hills, 2011; Jenkinson et al., 2011).

One potentially promising intervention has been successfully applied in a single case study. Fotopoulou and colleagues (2009) used a single-session of self-observation in a

video-replay and reported the instant and permanent reinstatement of motor awareness in a patient who was previously showing severe AHP. Unfortunately, these observations have not been as yet replicated in other patients and the intervention protocol has not been standardised. The main aim of this study was to test the feasibility and effectiveness of a general video-feedback intervention for anosognosia for hemiplegia in acute and chronic AHP patients in different hospital settings, as well as to explore the variations of the intervention protocol so as to optimise its effectiveness. Different parameters of this method were applied to the two patients based on their own neuropsychological profile, setting and rehabilitation needs, consistently with the aims of the study and the applied single-case design. To this end, the present results provide confirmatory evidence for the restoration potential of video-based, self-observation in AHP but also suggest a number of areas that require modification and further exploration.

Both patients in the current study showed indications of a sudden and unprecedented realisation of their motor impairments immediately following the video (e.g. ED: *"I can't move on my own. I wish I could, but I can't."*, FG: *"We have to work hard!"*, referring to his rehabilitation). However, unlike in the original study (Fotopoulou et al., 2009), their awareness scores on the standardised and experimental measures used post-intervention did not reveal a corresponding, complete and generalisable recovery of awareness as compared with their pre-intervention scores. Instead, the video viewing seemed to be only the first step in a longer and more complex rehabilitation process that required additional sessions (in the case of ED), several follow-up assessments (in the case of FG) and the provision of emotional support following and in-between sessions (both patients). In the case of FG for example, there was an immediate change in awareness following the video replay, but these results only become statistically significant after approximately 2 weeks. This indicates a gradual and steady improvement of awareness over time, which was first initiated by the video replay. Moreover, the noted improvements in the awareness of upper limb paralysis following observation of the upper limb in the video did not lead to a more generalised awareness of the patients' disabilities in uni-pedal or bi-pedal tasks. These required the passage of time and several, specific assessment sessions in the case of FG and a video intervention specifically targeting lower limb function in the case of ED. In both cases, unawareness for ADL's, especially involving crucial lower limb abilities (e.g. walking), proved to be more resistant.

Previous studies have found AHP patients to overestimate their ability more on bipedal than bimanual actions (e.g. rowing a boat or jumping up). This difference may be explained by the fact that acute patients have less opportunities to attempt bipedal than bimanual tasks in the hospital, as well as by the fact that the practical and psychological implications of bipedal movement deficits (especially walking and driving a car), are potentially more catastrophic and thus harder to accept or acknowledge (Marcel et al., 2004). Moreover, since in the current study the effects of the video intervention on upper limb awareness did not prove to automatically generalise to other domains, it is suggested that video intervention should progressively target AHP for different modalities: (1) AHP for upper-limb weakness, (2) followed by lower-limb unawareness, (3) and finally unawareness for ADL's. Furthermore it is important to recognise that the intervention suggested here is not a "method" in the sense of a rigid procedure that needs to be followed in an identical way with all patients. Rather, it represents an approach that is identical in its construct (represented in Figure 6.1), but also needs to be adapted to each individual specific condition (e.g. in the number of sessions, emotional support, limbs targeted etc.). Such variability in methods and the individualisation of approaches can be considered as an advantage of early-stage clinically-orientated research following stroke. This represents a fundamental principle of good practice in rehabilitation, and has been recognised in complex syndromes like anosognosia, where the importance of the individualisation of the rehabilitation approach has been emphasised (Prigatano & Morrone-Strupinsky, 2010).

Furthermore, it should be noted that video-observation brings about strong negative emotions in patients who otherwise deny their deficits and may appear as indifferent. This observation is consistent with findings from the original study that showed that awareness improvement was not accompanied by any changes in performance on neuropsychological tests of cognitive function but rather with a large increase in depressive feelings as captured by a self-report measure. More generally, the role of negative emotions and 'catastrophic' reactions (Turnbull et al., 2005; also see Chapter 3) needs to be taken into account in future protocols and perhaps more formal and longer sessions of emotional support need to be provided to patients. Whether these awareness-related emotions are a primary manifestation of the disorder itself, or a secondary consequence of other primary causes has long been debated in the literature (see Chapter 3 for discussion). This study cannot directly address such debates, but it nevertheless suggests that taking patients emotions into account may be an important component of

any successful intervention for AHP (see also Prigatano, 2005), as also shown in similar syndromes such as confabulation following acute frontal damage (see Fotopoulou, 2008) and unawareness in generalised and neurodegenerative disorders such as dementia (Ownsworth, Clare & Morris, 2006).

In the case of FG, the same day as the video intervention, an other-referent video was shown he was asked to comment on the “other” patient’s disability. FG showed greater awareness for motor disorders in this other referent condition than the self referent condition. In comparison, Ramachandran and Rogers-Ramachandran (1996) reported three cases of anosognosic patients, two of whom extended their denial of paralysis to another “stooge” student pretending to have left hemiplegia. Similarly to FG however, the third patient immediately recognised the motor deficits of the “stooge” patient. In comparison to the results in Chapter 5, patient FG’s anosognosia did not fully extend or generalise to the patient in the video, but there was no control group for comparison thus making the results unclear. However, FG was more aware in the other referent condition compared to the self referent condition, as shown in the experimental findings in Chapter 5. Furthermore, although the result of this study did show a greater trend of recovery over time for the self referent condition, the fact that he was more aware in the other referent condition to begin with, suggest that he had less of a margin for improvement. This again highlights the difference in the degree or severity of unawareness between self referent and other referent conditions as discussed in Chapter 5. Interestingly, “self” and “other” video replays have also been recently used as an effective treatment in increasing insight in schizophrenic patients (David et al., 2012).

6.5.1 Limitations and future research

Before firm conclusions can be drawn, it should be noted that this study has a number of limitations. Firstly, this study was limited to two single case studies. Furthermore, the lack of a control condition in both cases is a confounding variable in these studies. Accordingly, the results of this study need to be replicated in a carefully controlled group study, using a standardised protocol and also comparing the results with a control group. However, at this stage single-case study experimental designs offer an important and unique methodology for providing the appropriate empirical evidence for the effectiveness of the intervention (Perdices & Tate, 2009), and allowing for necessary calibrations before future, larger studies can be successfully designed. To the investigators knowledge, there are no previous larger trials of any intervention in this

population. There is also very little prior knowledge available in stroke research about the video intervention to be used. It was thus considered vital to evaluate the feasibility of applying this bedside intervention 'in the real world', as well as testing the acceptability of and adherence with the intervention and estimating important design parameters before planning larger scale studies, including a randomised controlled trial.

Furthermore, different intervention protocols were used in each case. The number of video observation sessions was different in ED and FG's intervention, and the results of ED's video intervention were restricted by a lack of statistical analysis. Nevertheless the basic methodology was the same for both patients, permitting them to be discussed together. Furthermore, the application of this protocol differed between both patients on the basis of specific factors. Specifically, for patient ED, the selectivity of her recovery (awareness for arm and not leg paralysis) that required specific video feedback of leg paralysis; her emotional reactions that required careful emotional responding; and her age, fatigue and cognitive profile made any further videos and assessments as those applied to Case 2 seem too demanding. In comparison to patient FG, where the general comments this patient made about his mobility did not necessitate a further video targeting any particular body parts. Furthermore, the different, more complex tests used to test the generability of the intervention was considered optimal in this patient, given the chronic stage of his anosognosia; finally, his age, cognitive profile and positive response to assessments, and the research as a whole, allowed for the use of an additional, other-based video, as well as more lengthily assessments.

However, it should be noted that it was not the intention of this study to suggest a generally applicable intervention for the rehabilitation of AHP, which may indeed differ from patient to patient and hospital to hospital. The general aim was to test the feasibility of the approach in two further patients, test its potential for awareness restoration in these particular patients, and examine particular extensions of the original protocol. The current study thus allows for calibration of the intervention and contributes important key practical, biological, psychosocial and organisational parameters that can lead to sufficient acceptability, adherence and effectiveness, and determine suitable subgroups in future studies (Arain et al., 2010). In clinical practice, the precise protocol for each individualised rehabilitation program is conditioned by personal and institutional variables. In the case of anosognosia, it seems pivotal to tailor rehabilitation goals and intervention strategies to suit the patients' particular cognitive, behavioural or sensory-

motor impairment (Perdices & Tate, 2009). For example, it is important to consider that not all patients may be appropriate for video intervention and that it is important to individuate the times when it is possible to suggest it. Moreover, severe spatial neglect that cannot be by-passed by prompting may prevent some patients from seeing left side of the screen when watching the video replay. Severe attention and memory problems may also reduce the effectiveness of the video observation. A preserved capacity for introspection and the ability to discuss one's emotions, may also prove to be important moderators of the intervention's effects. In all cases, these results suggest that in order to establish a good clinical relationship with the patient, it is not advisable to begin the intervention too soon after first meeting the patient.

Although it was not the aim of this current study, the potential difference and explanations in 1st and 3rd person perspective taking, and the off-line nature of video replay merit further investigation. Accordingly, future studies are needed to compare possible variations in motor awareness using both video replay and mirror feedback, in order to distinguish between online (observing one's actions while trying to move, as in the mirror) and off-line (self-observation while not trying to move, as in video replay) aspects. Lastly, although there was no change in neglect scores following the video-replay intervention, one cannot entirely exclude the possible casual effect of neglect. Attracting the patient's attention to the left side of space can temporarily restore neglect. Therefore, watching the video replay may have simply helped the AHP patient see their motor disability, and allow them to update the new information into long-term memory. Although double dissociations between anosognosia and neglect have been found (e.g. Davis et al., 2005), both syndromes are indeed complex and have varying clinical presentations. Therefore one can argue that double dissociations can be accounted for due to different types of neglect and anosognosia. However this wider question of the relationship between anosognosia and neglect is beyond the scope of this study.

Chapter 7 General discussion

7.1 Introduction

The general aim of the present thesis was to advance the current state of knowledge on the neurocognitive, emotional and social causes of anosognosia for hemiplegia (AHP). Based on insights gained from both clinical and recent experimental research on AHP (for reviews see Fotopoulou, 2012; Turnbull et al., 2014), this thesis has argued in favour of a methodological and a theoretical perspective shift. Specifically, it was argued (see Chapter 1) that a revision of purely cognitive theories of AHP is necessary. This new account of anosognosia moves away from traditional modular theories of anosognosia, towards a dynamic model of the construction of the bodily self. Accordingly, as outlined in Chapter 1, the thesis aimed to: (1) investigate the emotional and social factors that underlie motor unawareness in stroke patients; (2) identify the neurocognitive factors and neuroanatomical correlates that underlie motor awareness; and (3) develop potential, multifaceted bedside, rehabilitation interventions for AHP that target all the above factors.

These aims were achieved by using an integrative methodological approach, which combined neuropsychological testing, psychophysiological experiments and neuroimaging methods (see Chapter 2). A series of experimental studies (group studies and case studies) were conducted to address the overall aims (Chapter 3-6) with stroke patients with right-hemisphere damage. The experimental results of this thesis support the hypothesis presented in Chapter 1 that AHP patients live in an emotionally-laden, egocentric reality, where the ability to adopt a 3rd person perspective or the link between 1st and 3rd person thinking is defective. The neuroanatomical correlates of AHP found further support for the involvement of emotional and social factors in the aetiology of the phenomena. These findings on the role of emotion and social processes in AHP were in turn used to develop future rehabilitation strategies for AHP.

In this concluding chapter, the findings of the experimental studies will be reviewed collectively and revisited in relation to the proposed shift in perspective from purely cognitive theories of AHP to a new account of unawareness following right-hemisphere stroke, which integrates emotional and social factors. Current finding on self-observation using video replay as a rehabilitation intervention are discussed, as well as implications for future rehabilitation strategies. Subsequently, wider implications to theoretical debates

on the construction of the bodily self are discussed and general limitations presented. The thesis will conclude with tentative proposals for future avenues of research.

7.2 Summary and interpretation of experimental findings

7.2.1 Emotional processes in AHP

The possible role of emotion in AHP has long been debated between psychodynamic and neurocognitive theories. However, affective factors in anosognosia have been previously disregarded and insufficiently studied, with only a handful of cases studies focusing on this topic (e.g. Kaplan-Solms & Solms, 2000; Turnbull et al., 2005; Nardone et al., 2007). Therefore a specific aim of this thesis was to experimentally investigate the precise role of emotion in AHP. The study presented in Chapter 3 aimed to investigate how negative and positive emotions influence motor unawareness in anosognosia.

This is the first study to conduct a systematic, experimental investigation of the relation between emotion and motor awareness in right-hemisphere stroke patients with AHP. In this experiment positive and negative emotions were induced under carefully controlled experimental conditions in right-hemisphere stroke patients with AHP ($n = 11$) and HP controls with normal awareness ($n = 10$). The results of the study showed that motor awareness is sensitive to the induction of only negative emotions in a social context. The positive emotion induction has showed no effect on motor awareness. Lesion mapping methods, specifically lesion overlay and Voxel-Based Lesion Symptom Mapping (VLSM) approaches, were used to investigate the anatomical areas correlated with performance on the experimental task (i.e. change in awareness) following negative emotion induction. The insula ribbon, putamen and anterior periventricular white matter were identified as areas associated with less awareness change following negative emotion induction.

The results of this study suggest that anosognosia and the observed lack of negative emotions about motor weakness cannot be adequately explained by either purely motivational or neurocognitive accounts. Instead, it is speculatively proposed that lesions to such regions may impair interceptive signals and neuromodulatory pathways associated with motivation. Ultimately, such deficits result in an inability to update priors beliefs about the self and affectively personalise new sensorimotor information.

This experimental study contributes to understanding the intricate and often fluctuating clinical presentation of AHP patients, such as catastrophic reactions (sudden influx of negative or depressive feelings, Goldstein, 1939). As discussed in previous chapters, AHP patients usually do not present with catastrophic reactions or depressive feelings, but are typically overly positive or optimistic about their prognosis (Orfei et al., 2007). However, it has been observed in clinical case studies that following discussions of negative themes (not related to illness or paralysis), such as loss, separation or death, anosognosic patients present with a sudden influx of depressive feelings and related behaviours, together with transitory awareness about their illness (Kaplan-Solms & Solms, 2000). In comparison, the induction of negative emotion in a social context in the current study (the manipulation also being wholly unrelated to the prognosis) resulted in a similar experience of negative feeling and transitory awareness of motor deficits. These results also add confirmatory evidence to the proposal that recovery from anosognosia may lead to increased depression (see Fotopoulou et al., 2009). In this regard however, it is also important to highlight that depression maybe linked to impairments of executive functioning, which may in turn have an influence on unawareness (see Spalletta et al., 2006; Narushima et al., 1998). It is also important to acknowledge that specific studies have in fact shown the opposing results (e.g. Starkstein et al., 1992; Cocchini et al., 2013) reporting a weak relationship between depression and anosognosia. The question of hemispheric asymmetry of depression and anosognosia again comes in question here.

This study highlights a specific abnormality or over reactivity in the experience of negative emotion in AHP patients and its relationship with motor unawareness specifically. It is also inline with the proposed emotion regulation hypothesis (Turnbull et al., 2014). According to this hypothesis, in anosognosia the neurocognitive processes that control a higher-order mechanism of the regulation of emotions is compromised and therefore AHP patients present with abnormal emotional responses to events. The results of the current study show that there is a direct relationship between changes in emotion, specifically negative emotion, and motor awareness. In this respect the proposed damage to the emotion regulation mechanism in AHP influences how aware patients are of their motor weakness. Moreover, one possible hypothesis is that the more anosognosic patients experience the 'correct' or appropriate emotional response, the greater their awareness of their illness and related motor paralysis.

However this was only the first group experimental investigation in the role of emotion and anosognosia, and thus requires further empirical investigation. Future studies could add physiological measures to track changes in emotion (e.g. positive or negative emotion), rather than relying on only subjective reports from the patient. For example, automatic responses, such as heart rate variability, skin conductance and temperature changes, can be measured in response to the induction of emotions, while also measuring differences between behavioural and physiological responses to emotion related stimuli. Furthermore, other anosognosia phenomena that are directly related to emotional experiences have mostly been clinically described in the literature (see Cutting, 1978) and lack empirical study. For example, emotional indifference to illness and/or paralysis, first described by Babinski (1914) as anosodiaphoria, and extreme hatred for the paralysed limb (misoplegia; Critchley, 1974), have only been described as associated beliefs or disorders, but their exact relationship to anosognosia remains obscure. Babinski initially proposed that anosognosia and anosodiaphoria are in fact the same syndrome, but lie on a spectrum of severity with anosodiaphoria being a less severe presentation of AHP. However it has never been empirically shown if AHP gradually remises into anosodiaphoria or if this emotional indifference may exist without associated explicit denial of deficit. In contrast the presentation of misoplegia does not involve being overly optimistic or indifferent to ones deficits, as is common in AHP and anosodiaphoria, but the exact opposite emotional reaction. As Critchely originally described, misoplegia commonly co-occurs with AHP, but this apparent discrepancy in emotional experience is rarely clinically discussed or empirically studied. Only a handful of studies have reported single case's in adults (Loetscher, Regard & Brugger, 2006) and children (Moss & Turnbull, 1996), with the phenomenon only being clinically described but without complementary experimental investigations. Although both anosodiaphoric and misoplegic patients are a rare population group, there is still massive scope for future systematic studies on the exact presentation and mechanisms involved in these phenomena, and there relationship with anosognosia.

Interestingly, the proposed negative correlation between depression and anosognosia, and the experimentally demonstrated relationship between negative emotion and anosognosia in this current study, has similarly been found in Alzheimer's disease (AD). In AD low mood is associated with less anosognosia, while there is a greater emotional indifference toward deficits and the illness itself with increased severity of anosognosia (Mograbí & Morris, 2014). However, a causal relationship is yet to be shown between depression or

apathy and the severity of unawareness. Anatomically, there is evidence suggesting that apathy and anosognosia in AD are related to frontal lobe functioning as indicated by deficits in executive functioning as tested by neuropsychological assessments (Michon, Deweer, Pillon, Agid, & Dubois, 1994) and neuroimaging studies (e.g. Amanzio et al., 2011). Abnormalities in white matter tracts, specifically the anterior cingulate, has also been associated with emotional indifference in AD (Apostolova et al., 2007). Therefore, one can propose that the relationship between apathy and unawareness AD is not only regulated by frontal lobe functioning, but also by connectivity between the frontal parietal and temporal lobes. These anatomical correlates are strikingly similar to the neural correlates of AHP (see discussion in Section 7.2.4 of this Chapter), particularly the frontal lobes and white matter networks. Furthermore the anterior cingulate has also been implicated in error monitoring (Botvinick, Cohen, & Carter, 2004; Carter et al., 1998), which has been closely related to AHP by cognitive theories (Berti et al., 2005; Garbarini et al., 2012). This also speaks to recent experimental findings on the direct relationship between motor representations and emotion (see Chapter 3 for discussion; Gentsch & Synofzik, 2014). Taken together this may be indicative of a shared relationship between these phenomena, and emotional processes and error monitoring.

Furthermore, it was commonly observed by the investigator that during assessment sessions AHP patients often presented with behaviours (both verbal and behavioural), which could be interpreted as attempts to avoid questions in experimental tasks and clinical assessments. These avoidance behaviours presented in a variety of ways, including: misdirection (e.g. asking to use the bedpan or for some water; suddenly speaking about family or something entirely unrelated); omitting responses; using humour or irony to answer questions; minimising the extent of their motor weakness (e.g. *“Is their any weakness in your left arm?” “I suppose so, but I am not worried about it, as I do not use it much. It’s nothing I can’t get over.”*); exaggerating the ability of their right hand (e.g. *“I have always been stronger with my right hand anyway.”*); indirect or vague responses (e.g. *“Well I don’t know, I’m not sure. I guess I don’t think so.”*); and various behavioural responses (e.g. ignoring the examiner; physically turning away from the examiner; averting eye contact; and remaining silent and then “falling asleep” temporarily). It has been suggested that avoidance is a marker of implicit awareness of deficit (Prigatano, 2013, 2014), since avoidance requires knowledge of what is being avoided, perhaps implicitly. Within this context, denial in brain-damaged patients is considered to be a specific presentation of avoidance behaviour (Kortte & Wegner, 2004).

Avoidance in this respect is also defensive in that knowledge of deficits is upsetting therefore possibly motivating patients to remove such thoughts from conscious awareness. Unfortunately there are only a limited number of appropriate observer-based measures available to measure the construct of avoidance (Kortte et al, 2009). Future research will have to develop rating scales, based on these existing measures, to track avoidance behaviour in AHP stroke patients specifically. Future studies are therefore needed to systematically investigate these qualitative observations to understand the underlying mechanisms behind the presentation of avoidance behaviours and explore strategies to overcome avoidant behaviour in rehabilitation interventions.

7.2.2 Social processes in AHP

The study presented in Chapter 4 was the first to investigate the relationship between perspective taking, Theory of Mind (ToM; as two core modalities of social cognition) and self-awareness through the study AHP. More specifically, the study aimed to examine the role of visual-spatial perspective taking (VSPT) and ToM in self-awareness. First and 3rd person perspective taking abilities were assessed using both VSPT and ToM tasks, in patients with AHP compared to HP and neurological healthy controls. Patients presented with specific deficits in 3rd person perspective taking in both the VSPT and ToM investigations. There was also a strong correlation found between 3rd person perspective taking and executive functioning, particularly set-shifting abilities. Furthermore, the more severe the patient's motor unawareness the worse their performance in 3rd person perspective taking. Additionally, lesion-mapping methods identified brain areas commonly damaged in neurological patients in relation to VSPT and ToM behavioural scores taken from experimental tasks. The results showed that 3rd person perspective taking, in both the VSPT and ToM tasks, were significantly associated with frontal areas around the inferior and middle frontal gyrus (IFG and MFG) and extending temporally around the supramarginal gyrus (TPJ) and pre-and-post central gyrus, as well as dorsal frontal white matter. These anatomical correlates of AHP have also been identified as part of a 'mentalising network', specifically the supramarginal (TPJ) and pre-and postcentral gyrus (Koster-Hale & Saxe, 2013). This is the first study to investigate the relationship between social cognition and self-awareness. This study suggests that in anosognosia there is a specific deficit in ability to spontaneously disengage or integrate the 'self' – 1st person perspective and 'other' – 3rd person perspective, which is mediated by impairments in executive functioning and lesions to the IFG, MFG and dorsal frontal white matter.

The question of perspective taking was then further explored in Chapter 5 in a series of experimental investigations, which specifically examined perspective taking in relation to anosognosia-related material. It has been previously demonstrated that the presentation of motor awareness can be partial depending on if awareness questions were asked from the perspective of the patient referring to his/her paralysis (self referent) versus the motor weakness of another paralysed patient (other referent; Marcel et al., 2004; Moro et al., 2011). In these studies, AHP patients were more aware of the motor deficits of another paralysed patient compared to their own. In comparison, case-study investigations have suggested that at least some AHP patients are in fact also unaware of the paralysis of a “stooge” hemiplegic patient (Ramachandran & Rogers-Ramachandran, 1996). A limitation of such case reports is that they do not measure the degree or severity of unawareness. Therefore the patient can be mildly unaware of the other patient’s motor deficits, yet the degree or severity of unawareness differs (i.e. the degree of unawareness is not as severe as for their *own* motor deficits). The aim of the experimental investigations in Chapter 5 was to examine this partiality of unawareness in two ways: difference in 1st person versus 3rd person perspective; and (2) self referent versus other referent variances, together with difference in severity of unawareness for the self and other patient. Specifically, Experiment 1 investigated whether there were differences in anosognosia when asked from a 1st versus a 3rd person perspective in a self referent condition. Experiment 2 explored differences in 1st versus 3rd person perspective taking in an other referent condition, using a video of another paralysed patient. Lastly, Experiment 3 directly compared differences in motor awareness between self referent and other referent conditions using disability related ToM stories.

Results indicated that there were changes in motor awareness in relation to social or verbal perspective taking. AHP patients were more aware of their own paralysis when asked from a 3rd person (objective) perspective, compared to a 1st person (subjective) perspective. AHP patients were also unaware of the motor deficits of another paralysed patients shown in a video compared to HP controls, with no differences found when asked from a 1st versus a 3rd person perspective. However in comparing results of Experiment 1 and 2 it was observed that patients rated the severity of motor weakness for the other patient in the video as greater than their own motor deficits. Therefore indicating that although they are still anosognosic for the other paralysed patient compared to hemiplegic controls, in looking at the degree or severity of unawareness,

AHP patients were still more aware of the motor weakness and functional outcome of other paralysed patients compared to their *own* disabilities. In Experiment 3, both AHP and HP patients presented with overall deficits in disability related ToM stories. This confirms the results of Chapter 4 that right-hemisphere damaged patients, in general, have impairments in ToM tasks. More specifically, AHP patients again performed better in other referent ToM stories compared to self referent disability related stories. Therefore, AHP patients were more aware of the paralysis of the other patient in the story than their own motor weakness. Using lesion mapping methods, it was also found that lesions to the IFG, superior temporal gyrus (STG), insula ribbon, as well as subcortical areas (i.e. the thalamus, putamen and caudate) and dorsal frontal white matter, were significantly associated with the difference between other and self referent scores in the disability related ToM stories.

Taken together, results from Chapter 4 conclude that AHP patients have specific deficits in 3rd person compared to 1st person perspective taking in general social cognitive tasks. However, in comparison AHP patients were in fact better in 3rd person compared to 1st person perspective taking in experimental investigations presented in Chapter 5. Similarly it has been shown that AHP patients show dramatic improvement in body awareness when provided 3rd person visual feedback of their own body using videos (Fotopoulou et al., 2009; Chapter 6) and mirrors (Jenkinson et al., 2011). Here, there appears to be an apparent discrepancy in the ability of AHP patients to see reality from a 3rd person (objective) vantage point. Although the results of the current study suggest (Chapter 4) that AHP patient's social world becomes self-centred and egocentrically driven, it also appears that at some level these patients still have the cognitive capacity to draw on 3rd person perspectives (Chapter 5) depending on the context of the questions. However it is not suggested that AHP patients have a fixed or permanent deficit in 3rd person perspective taking (i.e. are completely unable to take on this perspective within any context), but rather there is a lack of spontaneous integration or updating of 1st person and 3rd person perspectives in anosognosia. The question here remains why AHP patients do not spontaneously integrate the 3rd person viewpoint, or possibly update their 1st person perspective on the body using knowledge from the 3rd person. Here, the content of the questions asked, or the wider social context in general, becomes crucial. As shown in Chapter 4, in visual-spatial or mentalising tasks that have a 'general' or non-specific content, AHP patients are egocentrically driven and tend to rely on the subjective, 1st person viewpoint. However one possible interpretation is that when presented with

disability related experimental tasks, which pose a potential threat to their current bodily representations, AHP patients spontaneously disengage from the 1st person perspective and assume an objective, 3rd person position. Therefore, it can be argued that anosognosic patients can be motivated or driven by the context of the question in an experimental manipulation, or the wider social context, to use a 3rd person perspective, but do not spontaneously integrate 1st and 3rd person perspectives in general. These proposals are however only tentative in nature and need to be validated by further experimental evidence.

These tentative proposals can also help explain why video feedback can lead to the successful remission of AHP. These results conclude that AHP patients do not spontaneously integrate or update perspectives, resulting in a discrepancy between their own (1st person) perspective on their body and the objective (3rd person) reality, which causes the presentation of anosognosia. Third person visual feedback and to a lesser extent conversations in the 3rd person, when presented in an emotionally safe environment (see Chapter 6), can facilitate an integration of perspectives causing AHP patients to update their bodily beliefs. Another speculative interpretation here is in line with advances in current research on spontaneous perspective taking - how persons spontaneously adopt another persons (3rd person) perspective among multiple environmental stimuli (see Furlanetto, Cavallo, Manera, Tversky, & Becchio, 2013). In a recent study, Furlanetto and colleagues examined what factors (e.g. eye gaze and action) influence spontaneous perspective taking of others by testing a large contingent of 120 healthy participants in two experimental tasks. Their results showed that when there were only objects and no other people in a visual scene, participants assumed a 1st person viewpoint. However when a visual scene included both another person and inanimate objects, participants were more likely to adopt a 3rd person perspective (i.e. the other persons viewpoint). This effect is then intensified by the other person interacting with the object (i.e. either looking at or reaching for the object). In a related behavioural study, Ambrosini, Pezzulo and Costantini (2014) conducted an action prediction task, finding that both gaze direction and arm movements from the actor in the task influenced participants' action predictions. Taken together these studies offer some insight into how the brain integrates multiple sources of information to influence spontaneous predictions. However, this question of spontaneous perspective taking is yet to be explored in AHP. It may provide an alternative explanation as to what information (e.g. 1st person versus 3rd

person perspectives; visual versus verbal feedback) is and is not being spontaneously integrated in anosognosia and in turn influences awareness.

However, the wider subject as to why AHP patients spontaneously recover over time comes to question. Anosognosic patients do not only encounter 3rd person viewpoints from simple experimental manipulations, but are confronted with this perspective through social and medical conversations and other daily occurrences (e.g. mirror viewing during physiotherapy or routine grooming). These continued social interactions and subsequent confrontations with the 3rd person perspective may in time result in AHP patients gradually reintegrating 1st and 3rd person perspectives. This may also account for the apparent fluctuations in awareness often noticed in the clinical presentation of anosognosia over time. For example, it has been commonly observed during the patient recruitment phase of this thesis, that a number of patients make similar comments that *“the doctors tell me I have had a stroke, I’m not so sure”* or *“that’s what they tell me, I don’t think I had a stroke, but the doctors tend to think so”*. Here, patients can understand the 3rd person viewpoint, but do not spontaneously integrate this objective perspective into their own subjective reality. However, over time when asked the same question patients responded that *“yes, I think I had a stroke”* or *“I understand now that I’ve had a stroke”* showing that patients have the capacity to reintegrate perspectives. Why or how quickly this happens may be due to the social and visual stimulation of various perspectives in everyday activities or by experimental interventions, but may also be associated with brain plasticity and white matter connectivity. However, this thesis has argued in support of AHP being a multifaceted phenomenon, therefore it is not only deficits in perspective taking that can account for the presentation of anosognosia and consequently spontaneous recovery, but various neurocognitive and motivational factors. Therefore AHP can persist into chronic stages (> 4 months after onset) due to a number of interrelated causes, such the severity and location of brain damage (see Vocat et al., 2010).

In summary, this thesis has drawn on both behavioural and neuroimaging methods to demonstrate the tight relationship between social processes (e.g. spatial and mental perspective taking), together with related anatomical areas, and anosognosia. It has experimentally demonstrated for the first time initial clinical findings (see Kaplan-Solms & Solms, 2000) that AHP patient’s social world becomes egocentrically and narcissistically driven, and proposes that’s there is a specific impairment in the actual

faculty that allows for an integration of 1st and 3rd person perspective taking (see Fotopoulou, 2014). It has further demonstrated the relationship between visual-spatial cognition (as a modality of social cognition and perspective taking, see Vogeley & Fink, 2003) and anosognosia through both manipulating patients visual-spatial perspective in a non-motor task and visual viewpoints through video replay (also see Turnbull et al., 2014). However, future studies are needed to further specify this relationship between social cognition and anosognosia to understand the precise mechanisms and anatomical correlates of 1st and 3rd person perspective taking on the body.

7.2.3 Neurocognitive correlates

An additional aim of this thesis was to examine the neurocognitive correlates of AHP by using neuropsychological testing. Both neurological groups, AHP and HP controls, were assessed using a battery of bedside assessments, as described in detail in Chapter 2, which tested cognitive functioning in a number of domains. In all studies, there was no statistical difference between groups in age, years of education, and time of system onset and assessment interval. Furthermore, there was no impairment or difference between groups in pre-morbid IQ, long-term and working memory, orientation and general cognitive functioning in all studies. Therefore these factors cannot account for the presentation of anosognosia as they are comparable between groups in the current studies and in previous investigations (see Orfie et al., 2007 for review).

Both patient groups showed both visual and sensory impairments, with no significant difference being found throughout this study between groups. Similarly, both neurological groups presented with impairments in visual spatial neglect consistently in each study. Although there was no statistical difference found, there was however a trend toward significance in two studies (Chapter 4 and 5) between the AHP and HP group, with the AHP group presenting with more severe impairments. Here, it is important to recognise that although a strong correlation has been found between AHP and visual-spatial neglect (Orfie et al., 2007; Vocat et al, 2010), double dissociations have been found between neglect and AHP (Bisiach et al., 1986). Therefore co-occurrence of visual-spatial neglect and AHP cannot be indicative of a causal relationship.

In two of the empirical studies (Chapter 4 and 5) there were impairments in executive functioning in both groups, but the AHP group presented with significantly worse performance in executive tasks than the HP group. However, despite significant

correlations there were double dissociations found in some patients between executive impairments and AHP, and therefore cannot be indicative of a causal role in anosognosia. Additionally, in one study (Chapter 3) there was a significant difference in the HADS measure of depression, with the HP group being significantly more depressed than the AHP group. This is inline with the Chapter's experimental findings on the role of negative emotion and AHP, with depression showing a negative correlation with motor unawareness. However, this result was not replicated in larger group studies (Chapter 4 and 5) in this thesis and in previous investigations (Orfie et al., 2007; Vocat et al., 2010).

Lastly, in all three group studies (Chapter 3-5) impairments in proprioception were found in both the AHP and HP group, and there was a statistical difference between groups with the AHP patients presenting with more severe proprioceptive deficits. This result has also been confirmed in previous studies (Levine, 1991; Vocat et al., 2010; also see Orfei et al., 2007). Although proprioceptive loss cannot fully account for the presentation of AHP due to some patients presenting with anosognosia without proprioception deficits, it may still be an important indicator and contributor to the severity of unawareness symptoms, their potential for spontaneous recovery, and may also predispose patients to AHP when other contributing factors are present (e.g. loss of mental flexibility; Marcel et al., 2004; Orfei et al., 2007). Furthermore, proprioception involves sensory motor predictions about movement in the body, which in turn is related to internal predictions arising from within the body as opposed to exteroceptive signals (Fotopoulou, 2014). Here Fotopoulou suggests that proprioceptive deficits in AHP may contribute to a reduced ability to generate new predictions about their body, and consequently their potential for left-sided movements. However, it is likely that a combination of deficits involving the 'internal body', including proprioception and interoceptive sensations (see Craig, 2009 and section 7.5.1 of this Chapter), may lead to weak or faulty interoceptive signals about the current physiological state of the body, including motor abilities.

These findings are inline with the proposal that multiple factors underlie the phenomena (Jenkinson & Fotopoulou, 2010; Orfie et al., 2007; Vuilleumier, 2004). These results indicate that the presence of AHP also co-occur with other neurological and neuropsychological deficits, such as neglect, proprioception and dysexecutive syndrome. However, although there is a co-occurrence of specific neurological and neuropsychological disorders with anosognosia, this does not imply a causative role. No single neurocognitive deficit is enough to cause AHP, but rather a combination of a

number of deficits, including emotional, motivational and social factors, and brain damage to critical lesion sites (see discussion below) may result in the presentation of AHP.

7.2.4 Neuroanatomical correlates in AHP

AHP is most frequently caused by right perisylvian lesions, but is also reported in left-sided brain damaged patients (Cocchini et al., 2009). Lesions of the right posterior insula (Karnath et al., 2005) and premotor areas, including the IFG and MFG (Berti et al., 2005), have been selectively associated with AHP. More recent results point to additional, critical lesion sites including subcortical structures (basal ganglia, hippocampus, amygdala) and deep white matter tracts (Fotopoulou et al., 2010; Vocat et al., 2010; Moro et al., 2011). The current study used both classic lesion overlay methods, as well as a novel and advanced statistical approach, VLSM, to advance our understanding of the neuroanatomical correlates that underlie motor awareness.

In each of the group studies presented in this thesis (Chapter 3, 4, and 5) lesion overlay and VLSM approaches were used to investigate the brain lesions associated with the diagnosis of anosognosia. Clinical CT and/or MRI scans were acquired and used for each analysis comparing the AHP group to the brain damaged areas in the HP group. In Chapter 3, the scans of 15 right-hemisphere damaged patients (AHP = 8, HP = 7) were used for analysis. Twenty-nine scans were acquired and used in Chapter 4 (AHP = 15; HP = 14) and in Chapter 5 the scans of 38 patients (AHP = 19; HP = 19) were used for lesion mapping. In comparing the results of the lesion mapping across all studies, there was no statistical significant difference between overall lesion size of the AHP and HP group. However, the overall lesion size of the AHP group was still consistently larger in comparison to the HP patients. Lesion overlay results across studies also consistently identified involvement of both cortical and to some extent subcortical areas in the AHP group, comprising of the inferior and middle frontal gyri extending to the temporal cortex, insula ribbon and internal capsule, as well as dorsal frontal white matter. In comparison, the lesion overlay maps for the HP group mostly revealed more focal damage in mainly subcortical regions. Subtraction maps of the AHP group overlay from the HP group overlay across studies consistently identified clusters around the insula ribbon, the IFG and MFG. The STG was identified in Chapters 4 and 5, and specific subcortical areas were found across studies: the posterior basal ganglia in Chapter 3; and the head of the caudate, putamen and internal capsule in Chapter 5.

The VLSM approach is an advanced method that characterises the statistical relationship between tissue damage and behaviour on a voxel-by-voxel basis, regardless of the classification of patients into categorical groups or by implementing a cut-off for pathology (Bates et al, 2003; Rorden, Karnath & Bonilha, 2007). In using this VLSM approach to investigate the anatomical areas associated with AHP, continuous Feinberg awareness scores were used, as it provides a measure of the severity of unawareness symptoms. This statistical method was used across group studies in Chapters 3, 4 and 5. In comparing the results across all three studies, VLSM analysis using continuous Feinberg scores revealed that voxels within the insula ribbon, the IFG and MFG, extending to temporally to the supramarginal and superior temporal gyrus, as well as dorsal frontal white matter were consistently significantly associated with motor unawareness ($p < 0.05$). The internal capsule was also significantly associated with AHP in studies presented in Chapter 3 and Chapter 4.

These results are in support of previous lesion mapping investigations in AHP, while adding both confirmatory and novel empirical evidence. Firstly, the presence (lesion overlay results) and severity (Feinberg VLSM results) of AHP were associated with a range of cortical and subcortical areas that have been previously linked to anosognosia (Berti et al., 2005; Fotopoulou et al., 2010; Karnath et al., 2005; Moro et al., 2011; Vocat et al., 2010). The area that showed the maximum Z score across all studies was the IFG and later the MFG (premotor areas), which have been previously identified as the critical areas for anosognosia. Although to a lesser extent, the VLSM analysis also revealed lesions to the insula ribbon to be an important indicator of AHP. Interestingly, the anatomical evidence generated from this thesis is much aligned to the recent lesion mapping study of Korte and colleagues (2014). The authors Region of Interest (ROI) analysis showed a strong correlation between lesions to the right IFG and AHP. A secondary voxel-wise analysis confirmed these results, but also identified insula damage to be associated with motor awareness, although to a lesser extent. Furthermore their analysis showed that subcortical regions, such as the basal ganglia were not significantly associated with AHP. Although the current study did identify some involvement of subcortical areas, previous studies have shown and hypothesised a critical role of subcortical structures, and especially the basal ganglia (Small & Ellis, 1996; Fotopoulou et al., 2010; Vocat et al., 2010). Therefore future studies with larger numbers of patients

with basal ganglia strokes will need to specifically investigate the involvement of these and other subcortical structures with anosognosia.

Interestingly, the studies presented in this thesis consistently found areas in the temporal cortex to be significantly associated with AHP that has not previously been emphasised as key markers for anosognosia. Other studies (Vocat et al., 2010; Moro et al., 2011) have also found significant association in clusters around the supramarginal gyrus (TPJ) and STG, however damage to these cortical areas have not been integrated into current neuroanatomical models of AHP. Traditionally more emphasis has been placed on AHP resulting from damage to frontal-parietal areas (Pia et al., 2004), with more recent research highlighted the critical role of the insula and frontal areas around the premotor cortex. The results of this study do confirm these previous findings, but also bring to focus the importance to damage in temporal areas, especially, in around the STG and SMG, in contributing to the presentation of AHP in at least some patients. This is in line with our experimental findings of the relationship between anosognosia and social perspective taking, which has a well-established link to the both the STG and SMG (Abu-Akel & Shamay-Tsoory, 2011; Koster-Hale & Saxe, 2013).

Damage to white matter tracks and consequently the role of connectivity has also been a secondary hypothesis to more topological or cortical theories. Each VLSM analysis, as well as lesion subtraction analysis, in all three studies found consistent evidence of lesions around dorsal frontal white matter tracks to be associated with the presentation of anosognosia. Only two previous studies (Fotopoulou et al., 2010; Moro et al., 2011) reported damage to white matter in the AHP groups specifically using lesion overlay methods. However, in the current studies presented in this thesis it was unfortunately not possible to specify exactly which white matter tracts were damaged in the statistical analysis due to a number of reasons, including, poor quality of the clinical scans and small sample size. More advanced methodological approaches need to be used (e.g. Diffusion Tensor Imaging, DTI), which required high quality MRI scans, to be able to specifically identify which white matter tracts have been damaged.

However, from the current results of this study it is possible to make some preliminary predictions of specific white matter tracts involved, which are found in clusters highlighted by the analysis within the dorsal frontal white matter. Firstly, damage to the cingulum could obstruct communication between the frontal cortical areas to the limbic

system. This hypothesis could account for the emotional irregularities commonly observed in clinical presentation and shown by experimental studies (Chapter 3). Furthermore, damage to the cingulum also impairs the pathway between frontal, parietal and temporal areas, therefore connecting both traditional theories of frontal-parietal damage and current findings of more temporal damage associated with AHP. Secondly, lesions to the SLF I (Superior Longitudinal Fasciculus) could result in damage to the pathway connecting the medial frontal lobe (including the IFG and MFG) and supplementary motor areas to the dorsal parietal cortex and frontal eye-fields. This hypothesis provides further support of the importance of damage not only to premotor areas, but also account for the importance of connectivity between the premotor cortex and the parietal lobe in anosognosia. Although only speculative at this stage, this possible account of anosognosia as a disconnection syndrome draws together various neuroanatomical explanations of AHP. A similar hypothesis has been proposed for the relationship between apathy and Alzheimer's disease. Although evidence from neuroimaging studies indicates that cortical areas (e.g. frontal lobes) are associated with emotional indifference in AD (e.g. Amanzio et al., 2011), lesion evidence has identified white matter abnormalities to account for a disconnection between the frontal and temporal poles (Apostolova et al., 2007). In the same respect, the anatomical correlates of unilateral spatial neglect have been identified by most studies in clusters around the posterior parietal cortex (Vallar, 2001; Mort et al., 2003) and less frequently around the superior temporal gyrus (Karnath, Berger, Kuker & Roden, 2004). However, advanced DTI analysis has found direct evidence for frontal white matter pathways, connecting the parietal and frontal lobes, damaged in neglect patients (Thiebaut de Schotten et al., 2005). Further research is therefore necessary to further explore and confirm these hypotheses on the role of connectivity and white matter damage in AHP.

7.2.5 Implications for rehabilitation

The wider implications of this thesis have both theoretical and clinical significance. In terms of clinical significance, AHP has lasting negative implications for the management and rehabilitation of patients (see Chapters 1 and 6 for discussion). AHP is often a transient phenomenon with spontaneous recovery occurring within days or weeks from onset (Vocat et al., 2010). Yet the presence of AHP in the acute stage may significantly obstruct rehabilitation efforts and consequently impede long-term functional outcomes (Gialanella et al., 2005; Jehkonen et al., 2006). Furthermore, approximately 30% of AHP patients remain anosognosic beyond the acute (< 4 months) stage (Pia et al., 2004; Orfei

et al., 2007). Therefore, the rehabilitation of AHP in the acute and chronic stage can be of long-term therapeutic significance. Although recently some progress has been made in the management of AHP (Jenkinson et al., 2011, for review), to date no evidence based treatment exists.

A recent, bedside psychophysical intervention, namely self-observation by video replay, led to a lasting remission of severe AHP in an acute stroke patient (Fotopoulou, et al., 2009). Video-replay provides the AHP patient with visual feedback from a 3rd person perspective (from the outside, objective) and ‘off-line’ (at a time different than the one in which the patient initiated the movement). This rehabilitation intervention for AHP is in need of further validation and is in the feasibility stage. Accordingly, this procedure was adjusted and applied in a case series study in Chapter 6. This study aimed to investigate the feasibility, effectiveness and optimisation of video replay as a possible rehabilitation intervention for AHP in both acute and chronic patients.

This video-replay procedure formed the basis of two intervention protocols administered independently to two patients with severe AHP. The first study used multiple, successive sessions of video-based self-observation in an acute patient, targeting first the awareness of upper limb and subsequently lower limb paralysis. The second study used a single session of video-based, self- and other- observation in a patient at the chronic stage following onset. Both protocols also involved elements of rapport building and emotional support. Four specific research steps were presented as a guideline for the video-replay intervention, including: conducting an initial awareness assessment; editing a short video of a previous awareness assessment; video viewing; and lastly, the follow-up assessment (see Figure 6.1 in Chapter 6).

The results revealed that video-based self-observation had dramatic, immediate effects on awareness in both acute and chronic stages and it seemed to act as an initial trigger for eventual symptom remission. Nevertheless contrary to the results of the original case study (Fotopoulou et al., 2009), these effects did not automatically generalise to all functional domains. This study provides provisional support that video-based self-observation may be included in wider rehabilitation programmes for the management and restoration of anosognosia.

The results provide further support for the finding that video-based, self-observation can reinstate motor awareness in AHP, by providing 3rd person and off-line feedback. It further highlights that while this simple, psychophysical intervention seems potent, it may not be sufficient for awareness restoration in all patients and it needs to be embedded in wider and perhaps individualised intervention protocols. These protocols would involve the targeting and training of specific facets of awareness (e.g. awareness of upper and lower limb function) and the management of related emotions and self-perceptions. This conclusion is consistent with recent theories of AHP that suggest it is a multifaceted syndrome entailing a dynamic interplay between neurological and psychological components (Vocat et al., 2010; Moro et al., 2011; Fotopoulou, 2013).

In line with these findings, previous studies with schizophrenic patients and related disorders have also found that video viewing of themselves in previous acute psychotic states improves insight or awareness of illness (Davidoff et al., 1998). In a more recent study, David and colleagues (2012) tested whether there was a difference in improvement of insight after viewing self referent versus other referent (gender matched) videos. This study was conducted with 40 patients admitted with a psychotic disorder, where they watched either self referent or other referent (control) videos. All patients showed a significant improvement in insight or awareness scores regardless of the actor (self or other) in the video. There was a trend, but no statistically significant difference between self versus other referent video viewing. Similarly, the case series in Chapter 6 also integrated the experimental design presented in Chapter 5 using both self referent and other referent video replay as part of one intervention strategy. Accordingly, the patient was more aware of the motor deficits of the other paralysed patient in the video (as shown experimentally in Chapter 5), and it is possible to tentatively speculate that watching both the self-and-other referent video feedback influenced the patient's eventual symptom recovery. Taken together, these results are therefore in agreement with the findings of the potential for video viewing as a rehabilitation intervention for unawareness, however the question of the specificity of the effect in anosognosia, as in schizophrenia, is yet to be resolved.

However, the video-replay rehabilitation intervention is still only in the feasibility stage. Larger group studies and future clinical trials are needed to validate this approach and explore variations of its application in order to optimise its effectiveness. There is also a need to translate the experimental finding of this thesis, specifically emotional and social

factors, into future rehabilitation strategies. In particular, the unique role of negative emotion needs to be taken into account in the application of any rehabilitation intervention with AHP patients, as they may be particularly vulnerable of lapsing into depression. It may also be possible to use this knowledge of negative emotion and awareness recovery within a carefully controlled therapeutic environment, as part of a holistic rehabilitation approach. Importantly, social perspective taking, such as verbal 3rd person feedback or conversation in the 3rd person, may also assist in reintegrating the 3rd person (objective) reality into the 1st person (subjective) reality of the unaware patient. Furthermore the use of mirrors, which provides 3rd person (from the outside) and online (at the same time in which the patient initiated the movement) feedback can also offer a cheap and easy bedside therapeutic approach, similar to video replay. However, future studies are needed to tease apart the difference between providing offline (using videos) and online (using mirror) feedback.

Future studies will therefore need to further translate empirical data on emotional processes and social factors involved in motor unawareness into new and innovative bedside rehabilitation studies. The emotional and social factors in recovery from stroke are only just beginning to be recognised and studied (Eslinger, Parkinson & Shamay, 2002). The affective elements involved in AHP have been highlighted by the field of neuropsychanalysis, which combines principles from both neuroscience and psychoanalysis (see Solms & Turnbull, 2002). Kaplan-Solms and Solms' (2000) psychoanalytic observations of AHP patients described above provides a in-depth account of how to use neuropsychanalysis to produce psychoanalytic observations in understanding and therapeutically treating AHP patients. Prigatano and Morrone-Strupinsky (2010) similarly recommend the use of psychotherapy with patients who use denial as a defensive coping mechanism. Furthermore, a better understanding of the role of 3rd person visual (using mirrors and videos) and verbal (1st versus 3rd person) perspective taking can be integrated into strategies for rehabilitation interventions. For example, in working with confabulating patients, Fotopoulou (2008) proposes that conversations using a "3rd person" perspective with the patient may be an alternative method used for enhancing both therapeutic rapport and patients' awareness of brain-related injury. As discussions in the "3rd person" may be a powerful tool used in rehabilitation interventions, Fotopoulou (2008, 2010) also suggests that the social context of the anosognosia/confabulation and the patients' social environment are equally as important. Taken together, future studies should consider using a combination of

techniques, such as video and mirror feedback, verbal discussions in the 3rd person, other referent video replay and psychotherapy, if the patient is willing. It may be further beneficial to provide specific rehabilitation guidelines and strategies that are individualised for each patient (see Prigatano & Morrene-Stupinsky, 2010 and Jenkinson et al., 2011 for reviews).

7.3 Implications on theories of the bodily self

Overarchingly, this thesis has aimed to contribute to the wider question of how we construct the reality of our bodily self. For centuries this question of how best to conceptualise the self has been a topic of debate among philosophy, neurology, psychology and more recently neuroscience (see Feinberg & Keenan, 2005). To aid in the scientific study of the self, researchers across various domains have divided the self into several dimensions, starting from the early work of William James, who conceptualised the self as both the subject and object of experience (1890; also see Neisser, 1988 and Robins et al., 2001 for more recent models of the different levels of the self). As introduced in Chapter 1, a recently developed philosophical approach integrates interdisciplinary viewpoints by dividing these approaches into two important aspects of the self: the ‘minimal’ self and the ‘narrative’ self (Gallagher, 2000). The narrative self involves the collection of self-defining experiences across time (e.g. autobiographical memory, Conway, 2005) and is based on the development of the more basic minimal or bodily self. Accordingly, minimal self-awareness involves the perception and experience of the world through our bodies, unextended in time, and is comprised of both a sense of ownership (the sense that it is *my* body that is moving) and the sense of agency (the sense that *I* am the initiator of that action). The focus of this thesis has been on advancing our understanding of this embodied view of the self, specifically through the study of a disorder of body agency.

This thesis has presented the view that the bodily self, as in anosognosia, involves the interaction between exteroceptive, proprioceptive and interoceptive signals (Brugger & Lenggenhager, 2014; Tsakiris et al., 2007), but is also developed and exists in the presence of others (Fotopoulou, 2014). This ability to integrate multimodal signals into an egocentric (1st person) perspective forms the fundamental basis for how we become self-aware (Blanke, 2012; Vogeley & Fink, 2003). However in contrast, the bodily self does not develop in isolation but in the context of other people, which involves the ability to perceive an allocentric (3rd person) perspective. First-person perspective, both spatial and

mental, is essential for the perception of body agency and ownership (Vogeley et al., 2001). Typically AHP patients remain unaware when their ipsilateral arm is brought into their right visual field indicating a primary deficit in 1st person perspective taking. Yet, the results of this study (Chapter 5 and 6) have shown that unaware patients are aware of their left sided paralysis when confronted with either 3rd person visual (i.e. video replay) or verbal (3rd person or other referent) perspectives. Therefore, this thesis has experimentally demonstrated that there is a distinction between the egocentric (1st person) and allocentric (3rd person) perspective in the construction of the bodily self. This therefore also tentatively suggests that the integration between the two perspectives takes places developmentally (see Reddy, 2008). In close relation, the ability to disengage from a 1st person perspective and draw on the metacognitive ability to understand or infer thoughts of feelings to other people is often referred to as a Theory of mind or mentalising (Frith & Frith, 2007). As discussed previously, embodied cognition (1st person perspective taking) and social cognition (3rd person perspective taking) has received extensive empirical attention when studied independently. However, this study, for the first time, has found the importance of 3rd person perspective taking or mentalisation on the bodily self (Chapter 4).

Accordingly, the results of this thesis demonstrate that the development of body awareness is not only dependent on the 1st person perspective, but on a dynamic interplay between 1st – and – 3rd person perspectives. Therefore the proposed hypothesis that both cognitive and emotional processes allow for flexible perspective taking and the integration of perspectives (Fotopoulou, 2014) has now been confirmed by experimental evidence in this study. This proposal of the ‘mentalisation of the body’ (Fotopoulou, 2014) has also been confirmed by the lesion mapping studies of this thesis, showing that temporal areas in the proposed mentalising network (supramarginal gyrus and STG) are consistently damaged in AHP patients and are associated with both spatial and mental perspective taking results. Thus showing an overlap of neural networks for both embodied cognition and social cognition. It additionally confirms the proposal that our embodied experience of the world is not solely dependent on neural mechanisms, but is embed within the social context (i.e. our environment; Gallagher, 2008). From a developmental perspective, it has been argued that from the very beginning our understanding of the world is influenced by others and the social environment (Decety & Sommerville, 2003). Although this question of intersubjectivity has not been directly addressed by this thesis, it has implications for further research on the ability to

distinguish between the self and other, and consequently shared representations between the self and other.

Closely related to the above conclusion, are the implications of the present results for the field of affective neuroscience (Pankseep, 1998). The study of anosognosia serves as a powerful example of how neurological and behavioural deficits should be broadened not only to include emotional influences, but to recognise affective factors as primary causes. The results of this thesis provide confirmatory evidence to the longstanding debate on the lateralisation of emotion valance, confirming the unique role of the right hemisphere, particularly for the regulation of negative emotion (Chapter 3; see Craig, 2009; Davidson & Irwin, 1999; Turnbull et al., 2005). Although there has been conflicting evidence, it has been traditionally suggested that the lateralisation of brain damage plays a causal role for the onset of depression in patients (Carson et al., 2000; Robinson et al., 1984). Thus inferring an assumed dichotomy in the lateralisation of emotional processing: the left hemisphere for “positive” emotion and the right for “negative” emotion. However, the results from this study, together with previous findings (Turnbull et al., 2005), have shown that patients with right lateralised lesions can have the ability to experience a range of emotions, however the regulation of emotional processes may be compromised. Furthermore, this study highlights the relationship between affect and conscious awareness (see Panksepp, 2003) by identifying the neural correlates (insular and striatal regions) for not only motivation and interoception, but affective processing of bodily self-awareness. These findings are additionally in line with recent findings on the tight interrelation between emotion and the sense of agency (see Gentsch & Synofzik, 2014; see Chapter 3 for discussion).

In summary, through the study of anosognosia, this thesis has therefore contributed to the to philosophical, as well as neuroscientific and psychological understanding, of body awareness. Firstly, the thesis showed that emotions (negative emotion, in particular) can influence our sense of movement and agency. Importantly, it has also provided confirmatory experimental and anatomical evidence of the relationship between bodily self-awareness and social cognition. The results of this thesis further propose that there is in fact an interplay between cognitive and emotional aspects of 1st and 3rd person perspective taking on the development of the bodily self. In that we come to construct a sense of body awareness through the influence of others, and more specifically through 1st - and - 3rd person spatial and mental perspectives. These socially shared experiences,

together with neurobiological mechanisms, work together to form representations of the social construction of the self.

7.4 General limitations

The limitations of each specific study have been addressed in detail in the previous chapters and in the discussion above. However, there are wider limitations affecting the thesis as a whole that must be taken into considerations when drawing conclusions from this study. These limitations are in turn presented and discussed below.

Firstly, although larger than most group studies in AHP, the overall sample size for individual experiments is relatively small in comparison to other clinical neuroscientific studies. Furthermore, the participation of each patient in the entire series of experimental studies varied. Resulting in some patients participating in only one experiment, while others participated in all of the experiments. Ideally, the same cohort of patients would complete all experimental investigations, in order to reduce individual and clinical differences that make comparisons across experiments problematic. However, this was an unavoidable limitation owing to a combination of factors involved in working with acute neurological patients with a rare disorder, such as: medical complications; patient transfer and discharge; resolution of AHP; working around patients' time with other clinical services (e.g. physiotherapy or ward rounds); fatigue; and/or changes or additional experimental protocols being developed in latter stages of the study and therefore not being completed by patients recruited early on. However, previous empirical studies on AHP have been conducted with relatively small sample sizes (e.g. Berti et al., 2005; Fotopoulou et al., 2008; Fotopoulou et al., 2009; Jenkinson et al., 2009; Vocat et al., 2012), which demonstrates that important theoretical findings can be obtained with relatively small sample sizes that are comparable to the present research.

Additionally, fatigue and the level of arousal in working with acute stroke patients is often variable, especially in working with elderly populations. This might lead to possible fatigue effects on the patients overall performance. However, every effort was made to conduct testing sessions when the patient was alert and awake. Patients were tested over multiple testing sessions and randomisation and counterbalancing procedures were also followed that help counteract the possible effects. Furthermore, advancing age is also found to lead to general cortical atrophy (Mueller et al., 1998) with some specific brain areas affected more than others, such as frontal and temporal lobes, subcortical regions

(Raz & Rodrigue, 2006) and white matter tracts (Madden, Bennett, & Song, 2009; Mueller et al., 1998). However, in working with focal brain injury following stroke, it is almost unavoidable to draw on elderly population groups due to the risk factors of stroke (e.g. hypertension, diabetes, cerebrovascular pathology) that commonly occur with aging (see Torner, 2005). Nonetheless, the potential influence of arousal and fatigue, as well as age, on performance cannot be entirely excluded, although this limitation would apply to all studies using acute brain damaged patients.

When considering the neuroanatomical finding of this present study, a fundamental limitation was the use of clinical CT and/or MRI scans (see Lezak et al., 2012). These structural scans, although still useful, are often of poor quality and therefore have low resolution. A better alternative is to use structural MRI scans acquired for research purposes using a tailored protocol. Furthermore, in working with structural imaging, such as CT and MRI, these scans do not fully indicate exactly where the functional impairment occurs, since they show the gross pathology, such as edema (Betz, 1997; Kreisler et al., 2002). It is additionally important to recognise that brain pathology is often a dynamic phenomenon, consequently the time of onset, scan acquisition interval and time of neuropsychological testing must all be considered (Bode & Heinemann, 2002; Lezak, 2012). Although there was no statistical difference found between time of onset and behavioural results between groups in the current study, future studies can further investigate this dynamic interplay by scanning patients at different time intervals paired with multiple neuropsychological evaluations at different time periods. However, in working with a rare clinical population of acute stroke patients, often of an elderly age, makes scanning patients difficult, also many elderly patients do not meet safety requirements.

Furthermore, although the clinical presentation of AHP can vary considerable (see Chapter 1 and Chapter 5), the current study grouped together patients presenting with the various ‘subtypes’ of anosognosia. This was due to the infrequent occurrence of AHP. For example, patients with different degrees of severity were all categorised as anosognosic patients, and sub-groups of AHP patients were not used due the limited number of patients. However, the use of the Feinberg scale, which gives an indication of the degree of severity of unawareness, was used to correlate anosognosia with performance on experimental measures, as well as for the VLSM neuroimaging analysis. Future studies that have access to a larger number of AHP patients can consider dividing larger

AHP groups into sub-categories based on their various clinical presentation. Nevertheless, such grouping is not uncommon in clinical research, especially while working with rare patient populations, such as confabulating patients. However, this issue of ‘patient grouping’ also pertains to the wider debate of the value of the single case-study versus group studies (see Shallice, 1979; Caramazza et al., 1988; Vallar, 2000). It cannot be denied that the single-case approach in neuropsychology, has not only set the historical foundation of the field, but has made significant contributions to our understanding of behavioural and brain processes (Shallice, 1979; Caramazza et al., 1988). Group studies cannot escape the heterogeneity of neurological disorders, requiring results across various domains (e.g. age, lesion size, premorbid intelligence etc.) to be averaged. A consequent disadvantage for group studies being the use of broad categories to allow for larger group sizes, but that lead to the loss of clinically diverse presentations found in the single-case approach. Accordingly, this present study aimed to use both group and case-study methods, as well as conducting individual analysis on experimental results in group studies when appropriate. Nevertheless, group studies are essential for the advancement of anosognosia research, in that inferences cannot be entirely made based solely on data from isolated case studies and without comparable control groups (Shallice, 1979). Group studies offer the added advantage of generating more accurate empirical evidence into brain-behaviour correlations (Damaseno, 2010). One alternative for future studies is to use multiple single case studies (as in Chapter 6) compared to suitable control patients or groups (Damasio & Damasio, 1997).

Lastly, the recruitment of patients from multiple hospital sites from both Italy and the UK, presents a range of limitations. Although the same clinical tests and experimental protocols were used, nevertheless assessments were conducted in both Italian and English. This wider issue of language and translation of tests can compromise both the validity and reliability of assessment measures (Artiola i Fortuny & Mullaney, 1998). However, most of the assessment measures used were standardised and validated for both English and Italian populations. However, due to the anosognosia being a relatively rare phenomenon, it was necessary to increase the number of hospital sites in order to recruit larger numbers of patients needed for group studies within a specific time frame. More broadly, this subject is related to the issue of the measurement of cognitive abilities across ‘racial’, cultural and ethnic groups (see Mackintosh, 1998), exploring how racial and ethnic differences may be contributing factors in brain development and organisation (Glymour, Weuve, & Chen, 2008). Therefore, in this respect there are substantial benefits

in conducting cross-cultural studies, which also allow for wider generalisation of results (Glymour et al., 2008; Pedraza & Mungas, 2008; also see Byrd et al., 2010). Accordingly, AHP cannot be mistaken as a culturally specific phenomenon, but rather as a prototypical disorder of self-awareness that transcends societal or cultural boundaries.

7.5 Directions for future research

Implications for future research have been specifically discussed in relation to each individual experiment in the previous chapters (see Chapters 3-6) and integrated into Section 7.2 of this current Chapter. However, this present study generates broader research questions that would be of particular interest for further investigation. These directions for future research are each considered in turn below.

7.5.1 Emotion and interoception

The role of emotion in AHP can be advanced by investigating how interoceptive bodily signals work together to produce a feeling of embodied self-awareness. There has been a recent advances in psychology and cognitive neuroscience by the influential discovery of a specialised interoceptive system that represents the internal, homeostatic state of the body (Craig, 2003). Interoception has been defined here as afferent signals that track the physiological state of all tissues of the body (i.e. the feeling that we perceive from our bodies), such as temperature, pain or pleasant touch (Craig, 2009). Consequently, the study of interoception is intimately involved in the study of emotion and self-awareness. Recent accounts of self-awareness have linked interoception with how we become aware of our bodies from within (Critchely et al., 2004; Craig, 2009). However, no study has looked at AHP, as a prototypical disorder of self-awareness, and the influence or impairment to the interoceptive system, in relation to any interoceptive modality (e.g. pain, temperature or pleasant touch). It has also been proposed that the anterior insula plays a crucial role in the representation of interoceptive signals. Interestingly, the role of the insula in AHP has been shown consistently in previous studies (see Karneth et al., 2005; Fotopoulou et al, 2010; Vocat et al., 2010) as well as the studies in the current thesis (see Chapters 3-5). Therefore theoretical proposals of interoception and neuroanatomical correlates on the insula both support future research on the relationship between interoception and AHP.

One specialised interoceptive modality is called pleasant or affective touch. Pleasant touch involves slow velocity stroking, which is coded by specialised (C-tactile) afferents,

found only on hairy skin (Olausson et al., 2002). Although only speculative in nature, in the current studies the investigator has noticed how patients themselves spontaneously engage in slow velocity stroking on their left (paralysed) arm by using their right hand. One patient in particular reported that her left arm was her “*alienated arm*” and only by “*loving and stroking*” her arm it would become hers again and “*correspond to her*”. These qualitative observations suggest that pleasant or affective touch, as a specific modality of interoception, is of particular interest for future experimental and physiological studies in AHP.

7.5.2 Body ownership disorders and other anosognosia phenomena

At the beginning of the thesis it was suggested that self-awareness, specifically the bodily self, involves both a feeling of ownership and sense of agency. This study has focused on AHP as a disturbance of body agency, however it was observed that the presentation of AHP commonly co-occurs with disturbances of body ownership, which includes both asomatognosia and somatoparaphrenia. Although this was a common clinical observation, the study of these additional anosognosic phenomena (Cutting, 1978) was beyond the scope of this thesis. Future studies, should firstly establish better assessment tools and specific diagnostic criteria for such body ownership disorders. Recent studies have shown preliminary evidence that anosognosia and somatoparaphrenia can be dissociable (Invernizzi et al., 2013; Brugger & Lenggenhager, 2014), yet it has been previously observed by larger group studies that body ownership disorders only occur with a simultaneous presentation of anosognosia (Marcel et al., 2004; Karneth et al., 2005). Future studies are needed to tease apart this intricate relationship between body agency and ownership disorders. Lastly, somatoparaphrenia, where patients attribute ownership of their arm to another person, often a close relative (Gerstmann, 1942), is better described in the literature (Vallar & Ronchi, 2009). Whereas asomatognosia, the inability to recognise one’s own body (Cutting, 1978), has not received the same empirical attention and its clinical presentation is ill described in the literature (Feinberg, Venneri, Simone, Fan & Northoff, 2010). Future studies need to better define the difference between the two disorders, develop better assessment methods and establish the association with these disorders and anosognosia, therefore contributing to a wider theoretical debate on the developmental progression of body ownership and agency.

In a recent review, Vallar and Ronchi (2009) described a classic taxonomy of disorders of body image. This classification includes a clinical disruption of patients to attribute undue

heaviness, dread or lifelessness to one half of the body (sometimes referred to as hyperschematia). Although possibly not directly related, patients recruited in this study often referred to their left paralysed arm as being “*dreadfully heavy*”, “*like a dead weight*”, or compare it to a “*rock*” or “*stone*”. Such qualitative descriptions of AHP’s patients paralysed left limb, as well as emotionally related phenomena, such as misoplegia and anosodiaphoria, merit more systematic assessment methods and future empirical studies.

7.5.3 Belief updating and AHP

It has been suggested that AHP can be compared to the development and presentation of delusions in other disorders (see Davies et al., 2005), which can reflect abnormalities in belief formation. It has also been suggested that beliefs are constantly updated in order to integrate new information and expectations, while at the same time adhering to an existing “web” of beliefs (Fotopoulou, 2014). More recent theories of belief updating and delusions are based on neurobiological principles known as predictive coding (Fotopoulou, 2014; Friston, 2009). Fotopoulou (2012, 2014) has provided an alternative model to explain the multifaceted nature of AHP using this Bayesian ‘predictive coding’ framework (Friston, 2010). This framework allows for a single and neurobiologically plausible formulation that incorporates both bottom-up and top-down mechanisms of perception and belief formation. In this context, AHP can be linked to a general antagonism between ‘prior beliefs’ (predictive internal models of the world based on previous learning) and ‘prediction error’ (discrepancies between expected and actual inputs based on interoceptive and exteroceptive signals).

Future studies can test this proposed model in respect to deficits in belief updating commonly found in AHP (Fotopoulou, 2012; Vocat et al., 2013). A recent study by Vocat et al. (2013) experimentally demonstrated that AHP patients tend to stick to their former beliefs and do not modify their original expectations, despite new evidence to the contrary, when asked to solve a simple riddle task. Future studies are needed to further explore this suggested fixation of prior beliefs. Furthermore, evidence from recent neuroimaging and lesion studies has suggested that the right IFG is selectively associated with deficits in updating undesirable information in non-anosognosic studies investigating unrealistic optimism in healthy participants (Sharot et al., 2012). Interestingly, as previously discussed in this study, damage to the IFG has also been consistently associated with AHP (Berti et al., 2005; Chapter 3-5). This neuroanatomical relationship

between belief updating and the role of the right IFG provides further evidence for the need to test these prediction in future interdisciplinary studies.

7.5.4 Neuroimaging analysis

Directions for future AHP neuroimaging studies have already been discussed in Section 7.2.4, however four key recommendations will be highlighted here. Although this thesis has drawn on novel methodological advances in lesion mapping, there are still more refined and advanced neuroimaging technologies that can be utilised in AHP research. Firstly, the use of better quality structural scans (e.g. research based MRI scans), rather than routinely acquired clinical scans, will enhance the accuracy of the lesion mapping results and allow for the use of more advanced programs (e.g. Matlab and Statistical Parametric Mapping; SPM) that allow for more sophisticated analysis. Secondly, using MRI scans to conduct white matter analysis to explore specific hypotheses surrounding the role of damage to white matter tracks and anosognosia. Thirdly, designing and implementing functional MRI (fMRI) studies will help test the role of various behavioural theories (e.g. emotional regulation; motor control and planning; motor observation; and social perspective taking) with anatomical correlates in AHP patients. Lastly, the scanning AHP patients at different time intervals using MRI scanners, will help track the patho-anatomical changes in the evolution of anosognosia symptoms from acute to post-acute stages. Therefore helping to resolve the long-standing question of spontaneous recovery in AHP.

To advance our understanding of the anatomical correlates of anosognosia, future research should take advantage of recent advances in neuroimaging methods. As discussed in Section 7.2.4 of this Chapter, the recent advent of diffusion tensor imaging (DTI) has allowed for the study of the anatomy of white matter tracts (Catani, Howard, Pajevic, & Jones, 2002; Thiebaut de Schotten et al., 2005, 2011). The use of DTI analysis can help uncover the role of connectivity and damage to specific white matter tracts in anosognosia. Furthermore, the majority of neuroimaging studies employ general linear models to examine the relationship between each voxel and a specific model or behaviour (Fox & Friston, 2012). Univariate approaches also suffer a general limitation in that they ignore the fact that no brain areas work in isolation (Carter et al., 2012). One alternative is to utilise a multivariate approach, which can investigate large-scale networks (Smith et al., 2014) and also facilitates analysis of multiple brain areas, as opposed to isolated regions. Taken together, future large-scale group studies on anosognosia that have the

necessary resources to acquire better quality MRI scan should draw on more advanced tractography and multivariant approaches to better understand both the white matter tracts and larger networks of cortical areas involved in motor unawareness.

7.6 Concluding comments

This thesis explored how we construct our sense of self, more specifically our bodily self, through the study of a prototypical disorder of self-awareness, AHP. More specifically, the present thesis aimed to examine the complex and dynamic emotional and social factors, and related neurocognitive and neuroanatomical correlates, involved in motor unawareness following right-hemisphere stroke. It revealed that AHP patients live in an emotionally-laden environment and egocentric reality, where there is an inability to spontaneously integrate or update 1st and 3rd person thinking, arising possibly as a consequence of damage to the inferior and middle frontal gyrus. These results were further confirmed by a potential overlap found in neural networks for embodied cognition and social cognition. Furthermore, these deficits in perspective taking lead to faulty inferences about the self and an inability to update premorbid beliefs about the body, which is mediated by brain lesions that impair interceptive signals and neuromodulatory pathways. This thesis has contributed not only to the advancement of our theoretical understanding of AHP, but has great clinical significance as well. The thesis has shown that social perspectives taking, as well as emotional and motivational processes, contribute to a dynamic understanding of AHP as a multifaceted syndrome. The translation of these findings has wider implications for the future treatment and rehabilitation of AHP.

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Appendices

Appendix A. Information sheet and consent form for neurological patients

Institute of
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King's College Hospital NHS
NHS Foundation Trust

Patient Information Sheet

Version 4: 25.05.11

Study Title: **Awareness of Illness Following Brain Damage**

Invitation Paragraph

You are invited to participate in a psychological study conducted at St. Thomas's Hospital and King's College Hospital. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you are currently unsure, you can think it over and let us know if you decide to take part any time in the following three weeks.

The Patient Advice and Liaison Service (PALS) is an organisation dedicated to offering information and advice to users of the NHS and can be contacted for advice on taking part in research. Your local office is located at:

- St Thomas' Hospital
Knowledge and Information Centre (KIC), ground floor, North Wing, Monday - Friday, 10am - 5pm.
Telephone: 020 7188 8801 or 020 7188 8803 or email pals@qstt.nhs.uk.
- King's College Hospital
Hambleton Wing, near the main entrance on Bessemer Road, Monday - Friday, 10am - 5pm.
Telephone: 020 3299 3625 or 020 3299 3601 or email kch-tr.PALS@nhs.net.

Thank you for reading this information.

1. What is the purpose of the study?

The overall purpose of this study is to explore and evaluate the subjective experience of illness following brain damage. Being aware of what has happened to you and how it may affect your future life is sometimes seen as a simple mental task. In reality, it is a very complex cognitive process (a mental ability) and one that has not been sufficiently explored by scientists. Crucially, some patients may partly or wholly lose such ability, if certain areas of their brain are affected. This study aims to investigate the neurological and psychological basis of such processes. More specifically, the purpose of the study is to understand how emotions and thoughts about oneself may affect one's perception of motor and visual difficulties and their everyday consequences.

2. Why have I been chosen?

In total, around 60 individuals will participate in this study. You, as well as the other participants, were chosen based on the type of brain dysfunction you have and particularly the site of the problem.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still

free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

According to your notes you have not participated in any other research, but please note that if you have been involved in any other research project, you should not take part in this study.

4. What will happen to me if I take part?

You are asked to take part in this study by participating in different psychological studies and tasks. These will take place in four to six different sessions, which will last a maximum of an hour each and will be scheduled, at your convenience, on non-consecutive days. In the first session you will be encouraged to describe the experience of your neurological illness and give its history. A number of standard cognitive tasks of memory, attention and problem-solving will also be administered in the subsequent. For example, you will be asked to complete a number of tasks concerning knowledge (e.g. defining words), thinking (e.g. interpreting proverbs), attention (e.g. identifying common patterns in figures), memory (e.g. recalling pictures) and body awareness (e.g. questions about your body). In the following sessions you will be asked to answer a number of questions regarding your present emotions and the view you have of yourself following your illness. Later, you will be asked to perform certain cognitive tasks such as completing sentences, and memorising words or phrases. You need to be concentrated in order to complete these tasks. In subsequent sessions, we will explain the details of certain of the administered tests in ways that we will not be able to reveal until you have completed the tasks. If you wish you may also ask for feedback on your answers, although the full results of the study will not be available at that stage. Your answers may be audio- and video- recorded. If out-patient appointments are arranged (subject to your agreement and convenience) we will reimburse your travel expenses to and from the hospital.

Please note that these sessions are independent of your clinical care and treatment, and they should not interfere with the latter at any stage and for any reason. Please also note that they are not needed for your care.

5. What are the possible disadvantages and risks of taking part?

There are no anticipated risks involved in this research, but if you should experience mental and/or physical fatigue, or any form of psychological distress please be aware that you could inform the investigator immediately and discontinue the session or even the study, if you wish and without consequences.

6. What are the possible benefits of taking part?

There is no direct benefit to yourself from taking part in the study. The information we get from this study may help us to understand and treat future patients with similar brain damage better.

7. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. All audio- and video- recordings made will be suitably anonymised, securely stored and made accessible only to the investigators. Anonymous data will be extracted from these recordings and the tapes will be destroyed 3 years after the completion of the study. Anonymous data will be retained for 5 years following their potential publication.

In the process of checking that this study is being carried out properly and the data collected is correct, authorised individuals (monitors or auditors) who may be employees of the company funding this research, or employees of external bodies, the ethics committee or regulatory authorities, may be granted access to any information held about you. This includes medical information and medical records. Anyone granted such access will also treat the information as highly confidential. By signing the consent form you agree to this access.

We will place a copy of this information sheet and a copy of the signed consent form in your hospital notes.

8. What if new information becomes available?

Sometimes during the course of a research project new information becomes available. If this happens we inform the Ethics committee. If there is any substantial change the forms and information given to volunteers will be modified from the original used in previous volunteers. We are a leading establishment in this area of research and if any new information relevant to this study becomes available the researchers will discuss this with you. You are free to withdraw from the study at anytime.

9. What will happen if I don't want to carry on with the study?

If you withdraw from the study we will destroy all identifiable information about you. We will retain and continue to use any data collected before such withdrawal of consent unless you request that you do not want us to use any data collected from you.

10. What will happen to the results of the research study?

The results of the research will form the basis of future scientific papers. These will be submitted for publication approximately one year following the completion of the study. Your identity and the confidentiality of your answers will be protected.

11. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

12. Who is funding the research?

The study is funded by two Volkswagen Foundation Grants and is sponsored by the Institute of Psychiatry.

13. Who has reviewed the study?

The study has been reviewed by the South East London Research Ethics Committee.

14. Contact for Further Information

If you have any questions regarding this study, or concerns regarding the manner in which the study was conducted or would like to be informed of the results when the study is completed, please feel free to contact the investigators:

- **Address for all communications:**

Dr. Katerina Fotopoulou

Academic Unit of Psychiatry, 3rd Floor, Block 8, South Wing, St Thomas's Hospital, London, SE1 8AZ. Email: a.fotopoulou@kcl.ac.uk. Fax: 020 7633 0061

CONSENT FORM

Version 3: 25.05.11

Study Title: **Awareness of Illness Following Brain Damage**

Please initial the following

1. I confirm that I have read and understand the information sheet dated(version) for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that the data collected during the study will be analysed and used in the final report and follow-up publications. However, I have been made aware that data will be anonymised.
4. I understand that sections of any of my medical notes may be looked at by members of the research team or regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
5. Do you understand that some of your answers in the study will be audio- and video-taped for scientific purposes? Do you consent to the unattributed and confidential use of these recordings for scientific purposes?
6. I agree to take part in the above study.

☐☐☐☐☐☐

Participant

Signed **Date**

(NAME IN BLOCK LETTERS)

Researcher

Signed **Date**

(NAME IN BLOCK LETTERS)

NB Three copies should be made, for(1) participant, (2) researcher, (3) hospital notes

Appendix B. Information sheet and consent form for healthy participants

Institute of Psychiatry

at The Maudsley

King's College Hospital 
NHS Foundation Trust

Department of
Psychological Medicine

Professor
Michael D Kopelman

Academic Unit of
Psychiatry
Adamson Centre
3rd Floor
South Wing, Block 8
St Thomas's Hospital
Westminster Bridge Road
London SE1 7EH


University of London

Tel +44 (0) 20 7188 5396
Fax +44 (0) 20 7633 0061

Information Sheet

Version 5: 25.05.11

Study Title: **Awareness of Illness Following Brain Damage**

Invitation Paragraph

You are invited to participate in a psychological study conducted at St. Thomas's Hospital. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you are currently unsure, you can think it over and let us know if you decide to take part any time in the following three weeks.

The Patient Advice and Liaison Service (PALS) is an organisation dedicated to offering information and advice to users of the NHS and can be contacted for advice on taking part in research. Your local office is located at:

- St Thomas' Hospital
Knowledge and Information Centre (KIC), ground floor, North Wing, Monday - Friday, 10am - 5pm.
Telephone: 020 7188 8801 or 020 7188 8803 or email pals@qstt.nhs.uk.
- King's College Hospital
Hambleton Wing, near the main entrance on Bessemer Road, Monday - Friday, 10am - 5pm.
Telephone: 020 3299 3625 or 020 3299 3601 or email kch-tr.PALS@nhs.net.

Thank you for reading this information.

1. What is the purpose of the study?

The overall purpose of this study is to explore and evaluate the subjective experience of illness following brain damage. Being aware of what has happened to you and how it may affect your future life is sometimes seen as a simple mental task. In reality, it is a very complex cognitive process (a mental ability) and one that has not been sufficiently explored by scientists. Crucially, some patients may partly or wholly lose such ability, if certain areas of their brain are affected. This study aims to investigate the neurological and psychological basis of such processes. More specifically, the purpose of the study is to understand how emotions and thoughts about oneself may affect one's perception of motor and visual difficulties and their everyday consequences.

2. Why have I been chosen?

In total, around 30 individuals will participate in this study. You, as well as the other participants, were chosen based on the fact that you do not have any known history of neurological trauma or disease. In other words, your brain is not known to be damaged. Your performance on the tasks explained below will be compared to that of neurological patients.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still

free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you may receive at the trust in the future.

4. What will happen to me if I take part?

You are asked to take part in this study by participating in different psychological studies and tasks. These will require from a minimum of one to a maximum of six different sessions, which will last a maximum of an hour and a half each and (if more than one) will be scheduled, at your convenience, on non-consecutive days. If you take part in a single session study you will be taking part in only one of the following assessments: a number of standard and experimental cognitive tests of memory, attention, body perception, and problem-solving will also be administered in subsequent sessions. For example, you will be asked to complete a number of tasks concerning knowledge (e.g. defining words), thinking (e.g. interpreting proverbs), memory (e.g. recalling pictures), body ownership (e.g. questions about your body) and attention (e.g. identifying common patterns in figures). During these tasks we will also measure certain physiological functions. The researcher will specify which one, show you the basic materials before you begin and will also give you a debriefing sheet that fully explains the study in the end. If you take part in the *entire* study you will be participating in all the tasks described above. In the session(s), you will be asked to answer a number of questions regarding your present emotions and the view you have of yourself. In the following sessions, you will be asked to perform certain cognitive tasks such as completing sentences, and memorising words or phrases. You need to be concentrated in order to complete these tasks. At the last session, we will explain the details of certain of the administered tests in ways that we will not be able to reveal until you have completed the tasks. If you wish, you may also ask for feedback on your answers, although the full results of the study will not be available at that stage. Your answers may be audio- and video- recorded.

Please note that these sessions are independent of any academic performance, assessment and any clinical care and treatment, and they should not interfere with these at any stage and for any reason.

5. What are the possible disadvantages and risks of taking part?

There are no anticipated risks involved in this research, but if you should experience mental and/or physical fatigue, or any form of psychological distress please be aware that you could inform the investigator immediately and discontinue the session or even the study, if you wish and without consequences.

6. What are the possible benefits of taking part?

There is no direct benefit to yourself from taking part in the study. The information we get from this study may help us to understand and treat future patients with similar brain damage better.

7. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. All audio- and video- recordings made will be suitably anonymised, securely stored and made accessible only to the investigators. Anonymous data will be extracted from these recordings and the tapes will be destroyed 3 years after the completion of the study. Anonymous data will be retained for 5 years following their potential publication.

In the process of checking that this study is being carried out properly and the data collected is correct, authorised individuals (monitors or auditors) who may be employees of the company funding this research, or employees of external bodies, the ethics committee or regulatory authorities, may be granted access to any information held about you. Anyone granted such access will also treat the information as highly confidential. By signing the consent form you agree to this access.

8. What if new information becomes available?

Sometimes during the course of a research project new information becomes available. If this happens we inform the Ethics committee. If there is any substantial change the forms and information given to volunteers will be modified from the original used in previous volunteers.

We are a leading establishment in this area of research and if any new information relevant to this study becomes available the researchers will discuss this with you. You are free to withdraw from the study at anytime.

9. What will happen if I don't want to carry on with the study?

If you withdraw from the study we will destroy all identifiable information about you. We will retain and continue to use any data collected before such withdrawal of consent unless you request that you do not want us to use any data collected from you.

10. What will happen to the results of the research study?

The results of the research will form the basis of future scientific papers. These will be submitted for publication approximately one year following the completion of the study. Your identity and the confidentiality of your answers will be protected.

11. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

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Dr. Katerina Fotopoulou

Academic Unit of Psychiatry, 3rd Floor, Block 8, South Wing, St Thomas's Hospital, London, SE1 8AZ. Email: a.fotopoulou@kcl.ac.uk. Fax: 020 7633 0061

CONSENT FORM

Version 3: 25.05.11

Study Title: **Awareness of Illness Following Brain Damage**

Please initial the following

1. I confirm that I have read and understand the information sheet dated(version) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the data collected during the study will be analysed and used in the final report and follow-up publications. However, I have been made aware that data will be anonymised. ☐
4. I understand that sections of any of my medical notes may be looked at by members of the research team or regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. Do you understand that some of your answers in the study will be audio- and video-taped for scientific purposes? Do you consent to the unattributed and confidential use of these recordings for scientific purposes? ☐
6. I agree to take part in the above study. ☐

Participant

Signed **Date**

(NAME IN BLOCK LETTERS)

Researcher

Signed **Date**

(NAME IN BLOCK LETTERS)

NB Three copies should be made, for (1) participant, (2) researcher, (3) hospital notes

Appendix C. Feinberg et al. (2000) Awareness Scale

| | |
|---|------------|
| 1 "Do you have weakness anywhere?" | |
| 2 "Is your arm causing you any problems?" | |
| 3 "Does it feel normal?" | |
| 4 "Can you use it as well as you used to?" | |
| 5 "Are you fearful about losing your ability to use your arm?" | |
| 6 "Is the sensation in your arm normal?" | |
| 7 "The doctors tell me that there is some paralysis of your arm. Do you agree?" | |
| 8 (Left arm is lifted and dropped in left hemispace.) "It seems there is some weakness. Do you agree?" | |
| 9 (Left arm is lifted and dropped in right hemispace.) "It seems there is some weakness. Do you agree?" | |
| 10 "Take your right arm, and use it to lift your left arm. Is there any weakness of your left arm?" | |
| TOTAL Responses for each item were scored as 0 if the patient showed awareness of deficit; 0.5 for partial awareness; and 1.0 for complete unawareness or denial. | /10 |

Appendix D. Patient demographic and medical history form

| | | | |
|-------------------------------|----------|------------------------------------|--|
| Code | | DOB | |
| Age | | Education level (years) | |
| Ward/Hospital | | Occupation | |
| Gender | | Hearing aids/glasses/other | |
| Assessors | | Handedness | |
| Date of onset | | Admission date | |
| Place of admission | | Referral [date & place] | |
| Inclusion criteria | | | |
| Unilateral lesion | R | | |
| <4 months | | | |
| Motor disorder | | | |
| Anosognosia | | | |
| Clinical notes | | | |
| Admission | | | |
| Circumstances | | | |
| Presentation | | | |
| Diagnosis | | | |
| Type of Lesion | | | |
| Scans done | | | |
| Radiology reports | | | |
| Neurological Exam | | | |
| Date & Description | | | |
| | | | |

| | | | |
|-------------------------------|--|--|--|
| | | | |
| Date & Description | | | |
| | | | |
| | | | |
| | | | |

| | | |
|----------------------------------|------------------------|--|
| Relevant Medical Info | Ethanol | |
| | Drugs | |
| | Smoker | |
| | Diabetes | |
| | Blood pressure | |
| | Family history | |
| | Sleep | |
| | Appetite | |
| | Past medical history | |
| | | |
| Medication | | |
| Psychiatric History | | |
| Family History | | |
| Social History (Optional) | Married/Divorced/Widow | |
| | Relationship | |
| | Children | |
| | "race"/culture | |
| | Place of birth | |
| | Hobbies/Interests | |
| | "religious" | |
| Mood (reported/observed) | Anxiety | |
| | Depression | |

| | | |
|-----------------------------|----------------------------|--|
| | Irritable/cooperative | |
| Speech | Fluent/Spontaneous | |
| | Monotonous | |
| | Impoverished/quality | |
| Clinical impressions | Appearance | |
| | Mood | |
| | Alert/Concentration | |
| | Avoidance | |
| | Egocentric characteristics | |
| | Other | |

Appendix E. Proprioception clinical protocol based on Vocat et al. (2010)

Proprioception is intact sense of position of the body and limbs- sign of normal primary sensory functioning. The protocol based on Vocat et al.'s (2010) clinical procedure.

ASK: *“Please close your eyes for me.”*

Then before each body part is moved, SAY:

“I am going touch your... (finger, wrist, elbow) to ask you which direction your... (finger, wrist or elbow) is moving, either up or down”.

Apply a small movement at the three joints [middle finger, wrist, elbow] listed below, in three separate attempts. Only touch the sides of the finger, wrist or elbow. Move them up or down and ask the patient to tell you what direction it is moving.

Rate the movements as:

0 Correct, mark as: ✓

1 Wrong, mark as: ✗

| Joint | 1 st Attempt | 2 nd Attempt | 3 rd Attempt |
|---------------|-------------------------|-------------------------|-------------------------|
| Middle Finger | | | |
| Wrist | | | |
| Elbow | | | |

Total score: /

Appendix F. Assessment for left-right disorientation

This assessment is designed to clinically assess left-right disorientation.

1. Lift the patient's right arm and ask:
Which hand is this?
2. Take the patient's left arm by the elbow and move the patient's hand into the right hemispace, and ask:
Which hand is this?
3. Ask:
Use your right hand to point to my left hand.
4. Ask:
Use you right hand to point to my right hand.
5. Point to the patient's right ear and ask:
Is this your right or left ear?
6. Point to the patient's left ear and ask:
Is this your right or left ear?
7. Ask:
Use you right hand to point to my right ear.
8. Ask:
Use your right hand to point to my left ear.
9. Touch the patients left leg and ask:
Is this your left or right leg?
10. Touch the patients right leg and ask:
Is this your left or right leg?

Appendix G. Table of groups' demographic characteristics and neuropsychological profile using non-parametric analysis

| | AHP(n=8) | | HP(n=8) | | Mann-Whitney Test | |
|---------------------------|----------|-------|---------|-------|-------------------|------|
| | Median | Range | Median | Range | Z-Score | P |
| Berti awareness left | 2 | 1 | 0 | 1 | -3.23 | 0.00 |
| MRC left upper limb | 0 | 1 | 0 | 1 | -0.52 | 1.00 |
| MRC left lower limb | 0 | 2 | 1 | 3 | -0.79 | 0.49 |
| Digit Span Forwards | 6 | 3 | 6 | 3 | -0.89 | 0.52 |
| MOCA memory | 3.5 | 2 | 4.5 | 2 | -0.83 | 0.56 |
| Comb/razor test left | 3.5 | 14 | 4.5 | 7 | -0.69 | 0.53 |
| Comb/razor test ambiguous | 5.5 | 5 | 4 | 8 | -1.41 | 0.18 |
| Bisiach one item test | 1 | 1 | 0 | 1 | -1.46 | 0.31 |
| Copy | 0 | 2 | 1 | 3 | -1.03 | 0.39 |
| Cognitive estimates | 18 | 14 | 16 | 6 | -0.94 | 0.37 |

Berti awareness interview= Berti et al. (1996); MRC= Medical Research Council (Guarantors of Brain, 1986); MOCA=The Montreal Cognitive Assessment (Nasreddine, 2005); Comb/razor test = tests of personal neglect (MacIntoch, Brodie, & Beschin, 2000); Bisiach one item test= test of personal neglect; Copy = conventional sub-test of Behavioural Inattention Test (Wilson, Cockborn & Halligan, 1987).

^a Scores below tests' cut-off points, or more than 1 SD below average mean.

*Significant difference between groups, $P < 0.05$

Appendix H. Experimental results of additional control experiment in Chapter 3

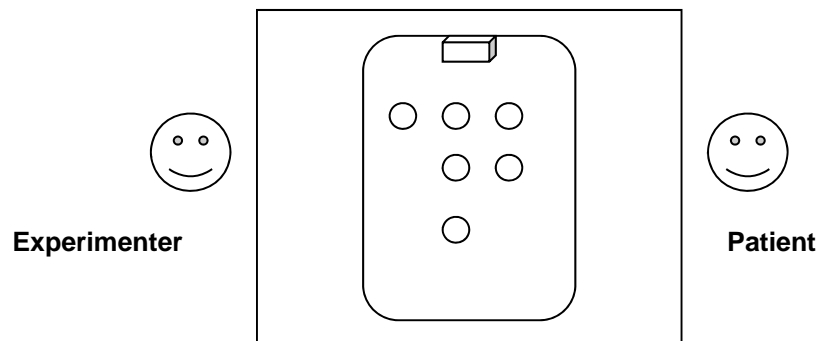
Experimental results of additional control experiment with 3 right-hemisphere brain damaged patients investigating change in visuospatial neglect, personal neglect and awareness of drawing neglect.

| Modality & Test | Patient | Positive | | Negative | |
|-------------------------------------|---------|----------|------|----------|------|
| | | Pre | Post | Pre | Post |
| Visuospatial neglect | | | | | |
| Line Bisection (Range:0-3) | | | | | |
| | HP09 | 3 | 3 | 3 | 3 |
| | HP10 | 0 | 0 | 0 | 0 |
| | AHP11 | 0 | 0 | 0 | 0 |
| Visuospatial neglect | | | | | |
| Star cancelation (54 omissions) | | | | | |
| | HP09 | 2 | 2 | 2 | 2 |
| | HP10 | 30 | 28 | 26 | 28 |
| | AHP11 | 50 | 50 | 49 | 50 |
| Personal neglect | | | | | |
| One item Test (Range:0-3) | | | | | |
| | HP09 | 3 | 3 | 3 | 3 |
| | HP10 | 2 | 2 | 2 | 2 |
| | AHP11 | 1 | 1 | 1 | 1 |
| Awareness of drawing neglect | | | | | |
| General questions (Range:0-2) | | | | | |
| | HP09 | 0.5 | 0.5 | 0.5 | 0.5 |
| | HP10 | 0.5 | 0.5 | 0.5 | 0.5 |
| | AHP11 | 0 | 0 | 0 | 0 |
| Awareness of drawing neglect | | | | | |
| Rating scale (Range:0-20) | | | | | |
| | HP09 | 4 | 4 | 5 | 5 |
| | HP10 | 14 | 3 | 15 | 12 |
| | AHP11 | 5 | 5 | 6 | 6 |

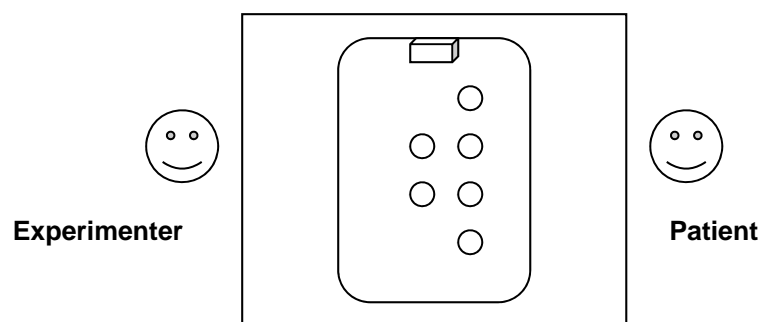
Bisiach one item test= test of personal neglect (Bisiach, Vallar, & Perani (1986); line bisection, star cancellation & copy & = conventional sub-tests of Behavioural Inattention Test (Wilson, Cockborn & Halligan, 1987)

Appendix I. Visual-spatial perspective taking task: example of visual arrangement

Example 1. Visual arrangements of position of cups on tray.



Example 2. Visual arrangements of position of cups on tray.



Appendix J. Control questions and arrangements for visual-spatial perspective taking (VSPT) task

Say:

“Now we are going to do something a little different. I am going to ask you a few questions involving this tray and cups. The questions will be about the position of the cups. I will ask you some questions about how you or I see the cups or about what pictures the camera might take. Do you understand?”

Then ask:

“Can you see the Camera?”, if they cannot see the camera, try to move it to their right visual gaze.

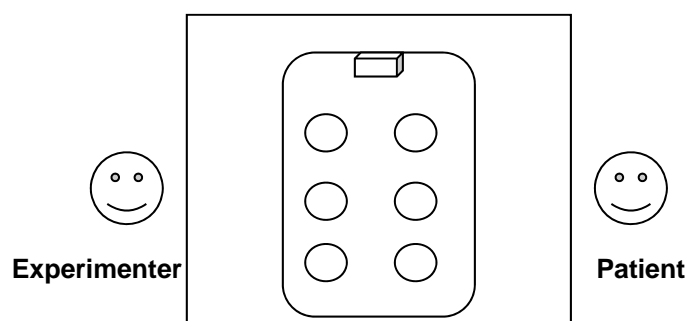
Then focus their attention to the tray and cups [how?], and ask, **“Can you see the tray and cups?”** Try and move the tray and cups until it is their full visual field.

Ask the following questions to confirm that the patient can clearly see the tray and cups:

“How many cups do you see?”, **“What colour is the tray?”**

Only continue after you have made sure the patient can see the tray and all the cups.

Set up the trays and cups as in the diagram below, again make sure the patient can see all the cups. **The camera should be on the RIGHT side of the patient.**



Appendix K. Examples of Theory of mind (ToM) stories from both 1st person perspective taking and 3rd person perspective taking set

| | Set 1 | Set 2 |
|--------------------------------------|---|---|
| Perspective | <i>1st person ToM story</i> | <i>3rd person ToM story</i> |
| Narrative | Late one night you are leaving the supermarket. You always get the bus home because you are afraid that if you walk home in the dark someone may attack and rob you. When leaving, you see a small child, about to walk home alone. You approach the child and ask, "Would you like me to walk you home?" | Lisa is terrible at returning books. Lisa often loses the books she borrows. Paul takes his book collection very seriously and would be very unhappy to lose a book. Lisa asks to borrow a book from Paul's collection, Paul replies, "Oh that one, it is not very good!" |
| 1st order question | Why do you say that? | Why does Paul say that? |
| Multiple choice questions | a) You believe the child may get robbed and attacked. b) You are making a joke. c) You want to rob the child. | a) Paul wants to discourage Lisa from borrowing the book. b) Paul does not like to read. c) Paul found the book terribly boring. |
| Extended narrative | The child has been warned by his parents not to talk or go anywhere with strangers, and tells you that he is fine on his own. | After hearing Paul's advice, Lisa thinks she now needs to choose another book. |
| 2nd order question | Why does the child think you offered to walk him home? | Why does Lisa think she needs to choose another book? |
| Multiple choice questions | a) The child thinks you are being nice. b) The child thinks you might hurt him. c) The child thinks you are old and confused. | a) Lisa thinks the first book is too long. b) Lisa thinks Paul suspects her of losing the book. c) Lisa thinks Paul does not think the book is very good. |

Appendix L. Full description of false belief control tasks used in Chapter 4

Task 1 – Age-adapted “Smarties” Task

A modified version of the “Smarties” task (Gopnik & Astington, 1988) was used. In order to make the experiment more appropriate for the target sample (i.e. elderly adults instead of children) the “Smarties” box (a box of sweets popular in North America and the UK) was replaced with a cigarette box, which was considered to be both age appropriate and easily recognisable. During the “cigarette” false belief task, participants are first shown a clearly recognisable cigarette box, which (unbeknownst to the participants) contained coins instead of cigarettes. Participants are then asked a control question “What do you think is inside the box?” and are expected to respond by stating the expected contents of the box (i.e. cigarettes). Answering this question correctly was a prerequisite to continue the task and is not included in the experimental questions below. Subsequently, the box is opened and emptied in front of the participants revealing that the content is in fact coins, showing that their initial belief is false. The coins are then returned to the box and the participants are asked a false belief question: “If your friend comes to visit you now, what will he/she think is inside the box?”. Participants are then asked two control questions: “What did you think was inside when I first showed you the box?” and “What do you think is inside the box now?”. As in the original “Smarties” task (Gopnik & Astington, 1998), a score of 1 was given for each question answered correctly and a score of 0 for incorrect responses (maximum score = 3).

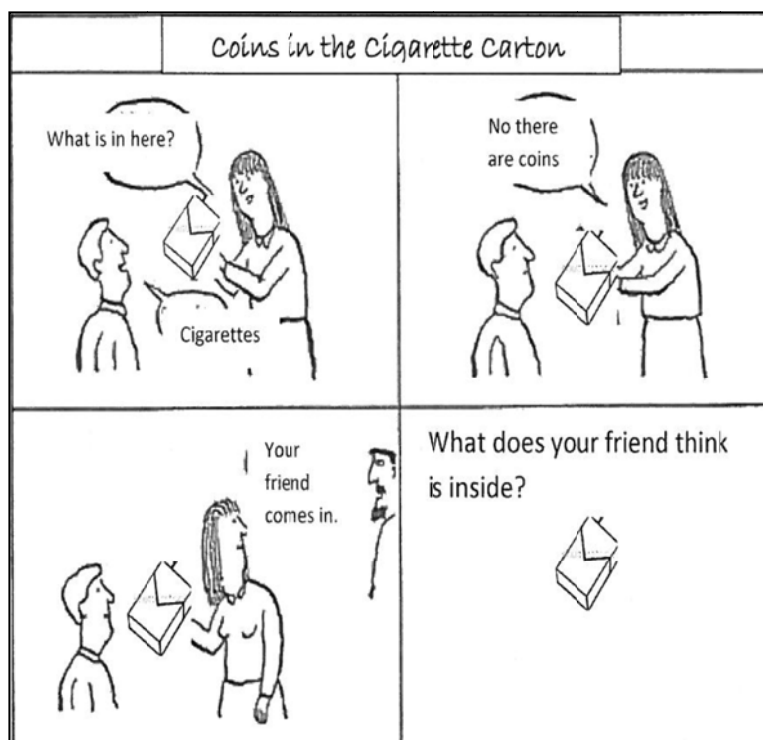
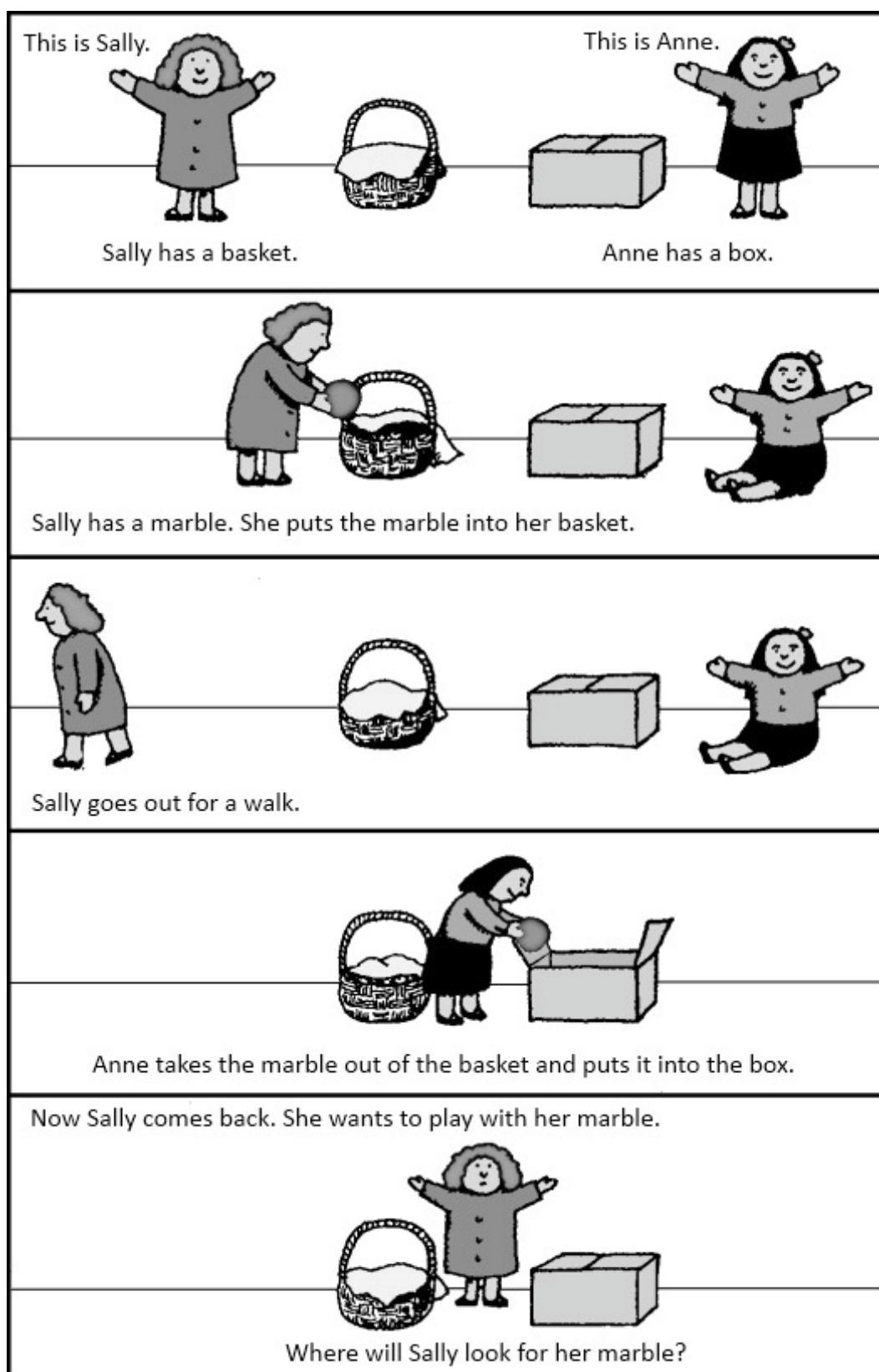


Figure L1. Example cartoon of scenario carried out in Task 1: age-adapted “Smarties task”.

Task 2 – The ‘Sally-Anne’ Task

Baron-Cohen et al.’s (1985) “Sally-Anne” false belief task was used. The procedure involves the presentation of five illustrations that make up a cartoon strip (presented on the right-visual field controlling for visual spatial neglect), which are accompanied by the experimenter giving a verbal description of the depicted events. The illustrations are shown on an A4 page with verbal descriptions following each scenario to guide the participant through the narrative. In the first scene the characters Sally and Anne are introduced, as well as a basket and a box. In the subsequent scenes, Sally hides the marble in a basket and leaves the scene. The cartoon then shows that while Sally is gone, Anne shifts the marble to a box. In the last scene, Sally returns. The participant is asked a belief question: “Where will Sally first look for her marble?” This is followed by two control questions: one reality control question, “Where is the marble now?” and one memory control question, “Where did Sally put the marble in the beginning?”. As in the original protocol (Baron-Cohen et al., 1985) a score of 1 was given for each question answered correctly and a score of 0 for incorrect responses (maximum score = 3).

Figure L2. Example of Sally-Anna cartoon used (Baron-Cohen et al., 1985).



Appendix M. Table of 3rd animate and 3rd inanimate conditions in visual-spatial perspective taking (VSPT) tasks

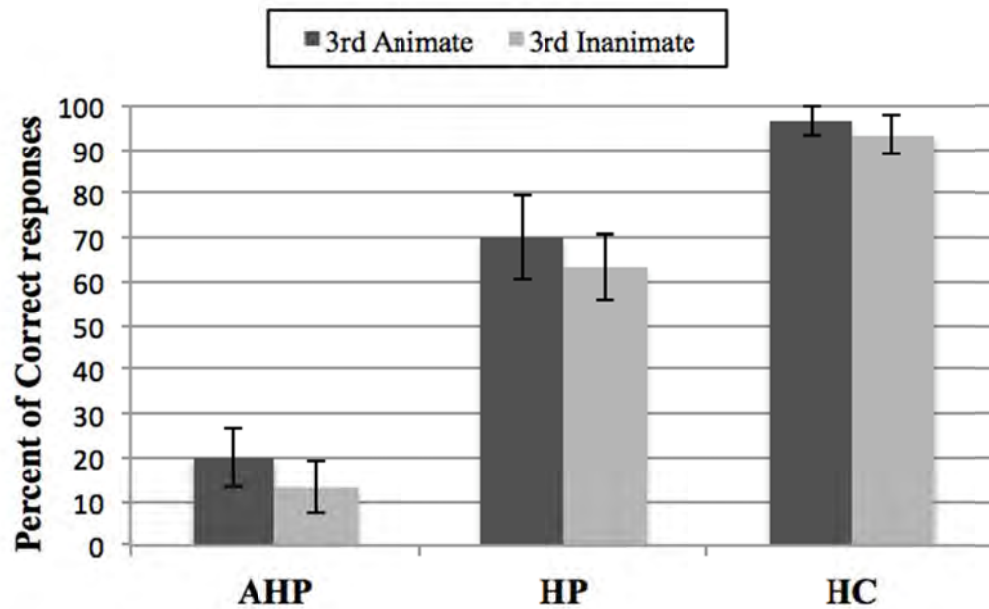


Figure M. Percentage of correct responses across groups (means and SE's) for 3rd animate and 3rd inanimate conditions. There was no significant difference within or between groups.

Appendix N. Examples of disability Theory of Mind (ToM) stories

| | Set 1 | | Set 2 | |
|--------------------------------------|---|---|---|---|
| Reference | <i>Self referent ToM story</i> | | <i>Other referent ToM story</i> | |
| Awareness | <i>Aware</i> | <i>Unaware</i> | <i>Aware</i> | <i>Unaware</i> |
| Narrative | <p>You are in the hospital, recovering from a recent stroke. You are very hungry and are looking forward to lunch. You can use your right hand, but you are still unable to use your left. The nurse delivers your lunch at twelve o'clock. You ask the nurse to cut your food.</p> | <p>You are in the hospital. The doctors tell you that you have had a stroke and that you are paralysed on the left side of your body. You are tired of sleeping and decided to sit in the chair instead. You try to get out of bed yourself, and fall down.</p> | <p>Amanda has just had a stroke and is recovering in the hospital. Amanda is left-handed, but her left arm and hand are very weak and she cannot use them. Amanda is very unhappy and bored in the hospital. The nurse, David, does not know that Amanda is left handed, and remembers Amanda has many friends who have sent her cards. He suggests she writes one of them a letter and gives Amanda a pen and some paper. Amanda gives back the paper and pen.</p> | <p>Samantha is in the hospital. The doctor says Samantha has had a stroke and that she cannot use the left side of her body. Samantha's friend Tom comes to visit her. Samantha immediately tries to stand and greet Tom. Tom rushes to Samantha's bedside to stop her.</p> |
| 1st order question | Why do you ask the nurse to cut your food? | Why did you fall down? | Why does Amanda not write a letter? | Why did Samantha try to stand? |

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| Multiple choice questions | <p>a) You think the nurse has nothing to do.</p> <p>b) You cannot use both hands to eat.</p> <p>c) You are feeling lazy.</p> | <p>a) The floor was wet and slippery.</p> <p>b) There was something wrong with the bed.</p> <p>c) You are not able to stand without help.</p> | <p>a) Amanda does not like the nurse and wants to upset him.</p> <p>b) Amanda cannot write, because she is left handed.</p> <p>c) Amanda is busy and has no time to write.</p> | <p>a) Samantha thinks she is able to stand and wants to greet her friend.</p> <p>b) Samantha does not like her friend and wants to leave.</p> <p>c) Samantha wants to walk to the bathroom.</p> |
| Extended narrative | The nurse is new to the ward, and knows nothing about your current medical condition. She kindly tells you that it is better for you to cut your own food. | The doctor is in the room when you fall and rushes to help you, reminding you that you should not try and stand without help. | Amanda thanks David, but tells him she cannot write the letters. | Tom tried to explain to Samantha that she must not try and stand without help, but she continues to tell him that she is well rested and will enjoy coming out of bed. |
| 2nd order question | Why does the nurse think you asked him/her to cut your food? | Why does doctor think you fell down? | Why does David think Amanda does not write the letter? | Why does Samantha think Tom tried to stop her? |
| Multiple choice questions | <p>a) The nurse thinks you simply do not like the exercise.</p> <p>b) The nurse thinks you cannot use both hands to eat.</p> <p>c) The nurse thinks you do not know how to use a knife.</p> | <p>a) The doctor thinks you are paralysed on the left and cannot stand by yourself.</p> <p>b) The doctor thinks the floor is wet and slippery and made you fall.</p> <p>c) The doctor thinks you are too tired and</p> | <p>a) David thinks Amada is too sad to write the letters.</p> <p>b) David thinks Amanda has no friends to write to.</p> <p>c) David thinks Amanda's paralysis left-</p> | <p>a) Samantha thinks Tom thinks she is too tired to stand.</p> <p>b) Samantha thinks Tom thinks she is paralysed on her left side and cannot stand.</p> <p>c) Samantha</p> |

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| | | cannot stand without help. | hand prevents her from writing. | thinks Tom doesn't like people to stand to greet him. |
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Appendix O. Case study 2: other referent condition additional methods and results

Clinical observations

At the end of the ‘other’ video replay, FG immediately commented: “*This man has to work hard, but I have to work more than him for rehabilitation.*” At the end of the video and in all subsequent sessions, the Judgement of Actions Test was used both in first and third person (for unimanual left and right, bimanual and bipedal actions) and the patient’s awareness recovery was monitored over time comparing self-referred responses and other-referred responses in the JAT.

Statistical analysis

In the other referent condition the same trend of results was hypothesised as in the selfreferent condition. Nevertheless, since we did not have a baseline measure, all the post video evaluations were compared with each other (i.e. 89 v. 90 , v. 103 and v. 113 days; 90 v. 103 and v. 113 days; 103 v. 113 days; one-tailed tests).

Results

BM responses showed a gradual increase of awareness (89 days = 5.00 (4.17 - 8.00); 90 days = 8.00 (6.17 - 9.82); 103 days = 4.50 (3.17 - 8.00); 113 days = 5.00 (2.17 - 7.82)). Statistical tests confirm the improvement in other-referred JATs for BM ($\chi^2(3) = 9.2838$, $p = 0.02575$) in particular after 90 days session, as confirmed by post-hoc tests (89 vs. 90: $W = 0.0$, $p = 1.000$; 89 vs. 103 $W = 23.0$, $p = 0.393$; 89 vs. 113 $W = 12.0$, $p = 0.278$; 90 vs. 103 $W = 33.5$, $p = 0.052$; 90 vs. 113 $W = 34.5$, $p = 0.052$; 103 vs. 113 $W = 15.5$, $p = 0.519$) (Figure 5). The improvement for LU actions (median (95% C.I.) 89 days = 4 (3.00 - 6.90); 90 days = 6 (3.30 - 7.90); 103 days = 4 (3.00 - 5.80); 113 days = 2 (2.00 - 4.00)) is not confirmed by post-hoc tests that do not show any significant differences between the single sessions ($\chi^2(3) = 9.2093$, $p = 0.02663$; post-hoc tests: 89 v. 90 $W = 0.0$, $p = 1.000$; 89 v. 103 $W = 4.0$, $p = 0.474$; 89 v. 113 $W = 15.0$, $p = 0.094$; 90 v. 103 $W = 6.0$, $p = 0.174$; 90 v. 113 $W = 15.0$, $p = 0.094$; 103 v. 113 $W = 8.5$, $p = 0.202$). BP (89 days = 5.00 (4.00 - 7.70); 90 days = 7.00 (6.10 - 8.00); 103 days = 5.00 (2.20 - 7.70); 113 days = 4.00 (4.00 - 5.90) and RU data (89 days = 10.00 (8.20 - 10.00); 90 days = 10.00 (8.00 - 10.00); 103 days = 10.00 (8.20 - 10.00); 113 days = 8.00 (8.00 - 10.00)) do not reach the statistical significance ($\chi^2(3) = 6.5745$, $p = 0.087$ and $\chi^2(3) = 2.5385$, $p = 0.468$ respectively).